VOLUME 15 NUMBER 3

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
FOR THE STUDY OF

INTERNAL SECRETIONS

EDITORS

R. G. HOSKINS, Boston

M. O. LEE, Boston H. LISSER, San Francisco

MAY-JUNE

1931

PUBLISHED BI-MONTHLY BY THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, SUITE 1214 WILSHIRE MEDICAL BLDG., LOS ANGELES, CALIFORNIA
ANNUAL SUBSCRIPTION, $6.00 SINGLE COPIES, $1.25

Announcement of New Publication

The Journal of Allergy

Editor—H. L. ALEXANDER, M.D., St. Louis

Associate Editor—WARREN T. VAUGHAN, Editor of The Journal of Laboratory and Clinical Medicine

Advisory Editorial Board

A. F. Coca, Editor of the Journal of Immunology; **Francis M. Rackemann**, Boston; **A. H. W. Caulfeild**, Toronto; **Albert H. Rowe**, Oakland.

A Real Need for This Journal

During the last decade Allergy has come to assume an ever-increasing clinical importance. Coincident with this growth, the literature on the subject is becoming very large and is to be found in medical journals throughout the world. Furthermore, there is every indication that allergy has far from reached its full development, either in its clinical or in its experimental aspects, and for this reason one may reasonably expect even more contributions to the subject in the future than there have been in the past.

Official Organ of Societies

The Journal is sponsored by the Society for the Study of Asthma and Allied Conditions, and by the American Association for Allergy. It has been elected the official organ for each of these national societies, which are the only ones devoted to the subject. The editorial board is composed of members chosen from these organizations. All papers read at the meetings of each of these societies will be published either in abstract or in their entirety. Other original articles will be published as they are submitted. In addition, there will be an abstract department which will select the best publications in the American and foreign literature. Considerable space will be devoted to this and our readers will find a service in this department alone that will be invaluable. Although the Journal will be primarily clinical in its aspects, pathologic and research material will be included when it is of distinct interest to the clinician.

What Subscribers Will Get

During the year, subscribers to *The Journal of Allergy* will receive between 650 and 750 pages of text, with about 600 words to the page. There will be sufficient well-chosen illustrations to go with and improve the original articles published. Besides these, 10 pages or more will be devoted in each issue to abstracts. *The Journal of Allergy* will be the only journal in any language devoted solely to allergy.

☛ **Only a limited number of Vol. I, No. I (November) have been printed. Subscribe now and secure the complete volume. They will become valuable.**

(Endocrinology)

THE C. V. MOSBY CO., 3523 Pine Blvd., St. Louis.

Gentlemen: Enter my subscription to the new JOURNAL OF ALLERGY. In United States and U. S. Postal Zone, $7.50. Foreign postage, $7.90. You may send me bill with first number.

Name.....

Address.....

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 15, Number 3 MAY-JUNE, 1931 Serial No. 77

ANTERIOR PITUITARY HORMONE IN THE BLOOD OF WOMEN*

4. A PRELIMINARY CLINICAL CLASSIFICATION OF RESULTS IN NON-PREGNANT INDIVIDUALS

C. F. FLUHMANN, M.D.
From the Department of Obstetrics and Gynecology,
Stanford University School of Medicine
SAN FRANCISCO, CALIFORNIA

The fundamental studies of Evans, Long, Smith, Engle, Zondek, and Aschheim demonstrating the ovary-stimulating properties of substances derived from the anterior lobe of the hypophysis have not only advanced our knowledge of the physiology of the female pelvic organs but have furnished the basis for an important laboratory test. This was first used by Aschheim and Zondek for the examination of urine and developed as a "pregnancy test," but studies conducted for the past three years in the Stanford Gynecological Laboratory have shown that the application of the Aschheim-Zondek procedure to the examination of the blood of women in non-pregnant conditions may yield results of important clinical significance.

The technique of the test has been described in detail in previous communications (Fluhmann 1, 2, 3) and consists in the induction of changes in the ovaries of immature mice by the injection of 5.0 cc. of blood serum from the patient. The finding of mature graafian follicles (Anterior Pituitary Reaction One, or APR I) in the test animals is considered as positive for the presence of the "follicle ripening" hormone of the anterior hypophysis (APH-A), while luteinized cysts or structures made up of lutein cells surrounding an ovum (APR III) denote the presence of the "luteinization" factor (APH-B). The present report is based on the results of the test performed in 280 non-pregnant women in whom no gross lesions of the pelvic organs could be demonstrated, and includes 178 cases used in the previous papers.

It would seem particularly desirable to develop a clinical classification based on the results of the test, which may be of use as a starting point for further similar studies or in determining the indications for "ovary-stimulating" or "ovary-substituting" therapeutic preparations.

*Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, June 8, 1931.

This study represents such an attempt, and in doing so it has been found impracticable to undertake a classification based on endocrinological diagnosis which seeks to determine the exact etiology of pelvic dysfunction. It was therefore necessary to resort to an interpretation of certain symptoms, and as a result it is possible to offer a grouping *in terms of ovarian function as determined by the history of the menstrual cycle.*

From this standpoint it is found that there are four main groups of patients (Table 1). In the first two (normal ovarian function; hypo-

TABLE I.

	APR I	APR III	APR I–III	Total Positive	Negative	Total
Normal Ovarian Function—						
Regular 28-day menses	0	0	0	0	45	45
Hypohormonal Conditions—						
Irregular delayed menses	1	0	0	1	29	30
Totally irregular menses	0	0	0	0	15	15
Scanty menses; regular cycle	0	0	0	0	16	16
Amenorrhea short duration	0	0	0	0	14	14
Amenorrhea long duration	0	0	0	0	16	16
Afunctional Conditions—						
Operative castration:						
a. Within 3 months post-op	8	0	0	8	12	20
b. After 3 months	13	0	0	13	4	17
Radiation castration	8	0	1	9	6	15
Post-climacteric	5	1	3	9	6	15
Amenorrhea long duration	5	1	4	10	0	10
Hyperhormonal Conditions—						
Menopause; irregular menses	9	0	2	11	22	33
Polymenorrhea	5	1	1	7	13	20
Dysmenorrhea (?)	2	0	1	3	11	14
	56	3	12	71	209	280

hormonal conditions) the test has been found negative, but in the other two categories (afunctional conditions of the ovaries; hyperhormonal conditions) it has been positive in a large proportion of the cases.

(1) *Normal ovarian function*—This group is the control series and includes 45 women who gave a history of normal menses and the pelvic examination in each case revealed no extensive disease beyond possibly a mild infection of the cervix, an uncomplicated retroversion, a Bartholin's gland cyst, etc. The blood examinations represent all stages of the menstrual cycle, and in each instance a negative reaction was found.

(2) *Hypohormonal conditions*—In this group, also characterized by a test negative for anterior pituitary hormone in the blood, are found five different clinical manifestations: (a) Irregular delayed menses, the interval between periods varying from 5 weeks to several months in length, and in most cases with a scanty flow; (b) Totally irregular menses, the interval being sometimes shortened, and sometimes lengthened; (c) Regular menstrual cycle, but with a scanty flow (oligomenorrhea); (d) Amenorrhea of short duration (from 6 weeks to 6 months); (e) Amenorrhea of over 6 months' duration.

(3) *Afunctional conditions*—The patients of this group are characterized by a total deficiency of ovarian function.* The number of positive tests obtained in women after operative extirpation of the ovaries increases rapidly in the first few weeks following operation so that after 3 months 76 per cent of the patients give an APR I, and this reaction has also been found as long as 14 years post-castration or 15 years after the menopause.

The inclusion of women following operative extirpation of the ovaries, radiation castration and following the climacteric as examples of total ovarian deficiency cannot be questioned, but some doubt may arise regarding the advisability of placing a number of patients with amenorrhea in this category. Of 26 women with periods of amenorrhea of over 6 months' duration† 10 gave a strong positive reaction, and clinically it was found that obesity was associated with the condition in 6 of the 10 cases, whereas in the 16 patients with a negative test obesity was noted only 4 times. The interpretation that the existence of a positive test here represents a total absence of ovarian function (temporary or permanent) is open to question and must be subjected to further investigation, but for the present this conception would seem to be a logical explanation for the occurrence of the positive tests. It is possible also that the presence of the hormone in the blood may be merely a phase of the disease and subsequently disappear. The prognosis in these cases must be considered as unfavorable but not hopeless, as at least two of the patients in this group have responded to treatment.

(4) *Hyperhormonal conditions*††—The findings in this group are not as definite as in the preceding since positive tests have been obtained in a smaller number of cases and in some instances it has been necessary to repeat the examination two or three times before the presence of anterior pituitary sex hormone could be demonstrated in the blood. It includes a number of younger women with too frequent and profuse menses, approximately one-third of the women of the menopausal age with menstrual irregularities (also chiefly polymenorrhea), as well as three isolated observations on patients with normal or profuse menses associated with marked dysmenorrhea.

DISCUSSION

In analyzing the results reported in this study, it is very important to remember that in contrast to the work which has been conducted on the presence of estrin (ovarian follicular hormone) in the blood at various stages of the normal menstrual cycle (Frank and Goldberger, Siebke, and

*The blood findings in patients of this group have recently been corroborated by Zondek (11) and Mazer and Hoffman (12).

†Twenty-four of these patients had a secondary and two a primary amenorrhea. One of the latter, a woman aged 20, gave a positive test. The second, a patient of Doctors Emge and Reichert, gave a negative test, but the cause of the condition was found to be a brain tumor compressing the pituitary body and producing an atrophy of the anterior lobe.

††This name must not be confused with the term "Hyperhormonal amenorrhea" which has been employed by a number of German authors and which refers to studies on ovarian hormone.

others), the present test is not sufficiently delicate to demonstrate the anterior pituitary hormone (or hormones) in the blood of the normal woman. A positive result is thus an indication of an abnormal condition, and shows an excess of these substances in the blood.

It is also of interest to note the relative occurrence of the two characteristic reactions of the test. The presence of the follicle-ripening reaction (APR I) is by far the more frequent of the two, and was found in all but three of the patients. However, the occurrence of APR III, the luteinization reaction, in 15 of the patients of this series, is worthy of special notice since this is the finding which forms the basis for the Aschheim-Zondek "pregnancy test." It is quite possible that when greater numbers of patients with endocrine disturbances are examined, the presence of this reaction will have a particular significance.

The group described under the term "hypohormonal conditions" is of special importance because it includes the patients who offer the most favorable prognosis for treatment with "ovary-stimulating" extracts of the anterior lobe or placenta. It has been customary in the past to refer to women with irregular, delayed, scanty, or absent menses as having a "hypo-ovarian" condition, but as more is learned about the interaction of pituitary and ovarian hormones, it would seem as if this conception must be held in doubt and that the majority of these patients actually have a primary "hypopituitary" disease. The negative tests in this category are thus in keeping with this viewpoint.

In the group of "afunctional conditions of the ovary," the test gave a large percentage of positive results. Although the demonstration of large amounts of anterior pituitary hormone in the blood of these patients is in keeping with the well-known castration hypertrophy of the anterior lobe and the reported increased potency of anterior hypophysial implants from spayed animals, the exact significance of this finding is not known. There are, however, two possible explanations. In the first place, the hormone found free in the blood and stored in the gland itself may not represent an overproduction but a non-utilization due to the absence of ovarian function. Secondly, the ovaries may have an antagonistic influence on the anterior hypophysis, and as a result of the cessation of ovarian hormone production this restraint is removed and the anterior lobe manufactures great amounts of its hormone which are then excreted.

The patients of the fourth group (hyperhormonal conditions) present a problem very distinct from those of the preceding since they give evidence of some ovarian activity instead of a total deficiency. It is, of course, impossible at this stage to give more than a theoretical explanation for the presence of large amounts of anterior lobe sex hormone in the blood, and it may in time prove necessary to place the patients of the menopausal age in a separate category. The problem of polymenorrhea, too profuse and too frequent menses, however, is a very vital one to the gynecologist, and there are three explanations for the production of this

condition. It is of some importance to mention these in detail, because the third suggests the existence of a primary hypophysial overactivity as the etiological factor, and thus offers an explanation for the presence of large amounts of anterior lobe sex hormone in the blood of some of these patients.

(1) These patients may not undergo a normal menstrual cycle but may have a "glandular hyperplasia endometrii," a condition which is characterized by a failure of ovulation with consequent lack of corpus luteum formation and an excessive production of the ovarian follicular hormone ("hyperestrinism"). Hofbauer (4) has recently brought forward evidence suggesting that a hyperfunction of the anterior hypophysis may result in hyperplasia endometrii, but there are a number of objections to accepting this theory at the present and these have been set forth in detail elsewhere (Fluhmann 5). It is felt that this is not the explanation for the positive findings in this group, and this conception is strengthened by two observations. In the first place, the existence of a hyperplasia endometrii was definitely disproved by a microscopic examination of the endometrium in two of the cases of this group with a positive test, and in a third instance by the demonstration during an exploratory laparotomy of a gross corpus luteum in one of the ovaries (Dr. L. A. Emge). And secondly, the examination of the blood of 10 proved cases of this disease has shown the presence of anterior lobe hormone in the blood in only one instance.

(2) The second possibility, which has been championed by R. Schroeder (6), is undoubtedly the explanation for the occurrence of most instances of too frequent menses and includes the patients with this symptom associated with pelvic inflammatory disease. It assumes that as a result of injury or an inherent weakness in the ovary there is a premature disintegration of the corpus luteum with a resultant early appearance of menstruation. From this standpoint, therefore, many of the patients with this complaint should be classed in the "hypohormonal" group, but if this conception is held as applying to *all* instances, the excessive amount of anterior pituitary hormone in the blood must be explained on the same basis as the "afunctional group," namely, that it is due to deficient ovarian function. Since this would be in direct contradiction to the negative findings of the "hypohormonal group," which represents a much more serious ovarian defect, there is a grave objection to accepting this theory as applying to those patients with polymenorrhea who have large amounts of anterior lobe hormone in the blood.

(3) The third possibility is based on the assumption that there is a speeding-up of all the events of the menstrual cycle, so that the whole process is completed in a shorter time than the usual 28 days. The pathological and clinical aspects of this type of patient where the ovaries show premature ovulation and the presence of numerous corpora lutea while the endometrium undergoes a more rapid development, has recently been

discussed by Shaw (7), Fluhmann (8), Meigs (9), and others. One of the patients of this group, whose blood on one occasion gave a strong APR I and who complained of prolonged and profuse periods occurring every three weeks, illustrates this possibility very well, as a diagnostic curettage on the 12th day of the cycle yielded endometrial tissue showing a degree of development which is usually associated with the 21st day. The presence of excessive amounts of anterior lobe hormone in the blood of some of these patients would thus suggest that there may here be a primary anterior hypophysial overactivity with an excessive production of its sex hormone resulting in a speeding-up and intensification of otherwise normal ovarian and uterine cycles. The work of Smith and Engle (10) with the prolonged use of implants in adult mice and rats seems to give experimental support to this possibility.

CONCLUSIONS

The examination of the blood of 280 non-pregnant women with no anatomic pelvic disease, for the presence of the anterior pituitary sex factors shows that patients may be grouped into four categories according to the results of the test.

(1) Normal ovarian function—The test has been found negative in patients with a normal twenty-eight-day menstrual cycle.

(2) Hypohormonal conditions—The test has also been negative in women with irregular, delayed, scanty, or absent menses. It would seem that this group offers the most favorable prognosis for treatment with "ovary-stimulating" extracts.

(3) Afunctional conditions—The presence of large amounts of anterior pituitary sex hormone has been demonstrated in a large percentage of patients with a total deficiency of ovarian function, such as occurs after operative extirpation of the ovaries, radiation castration, and in the post-climacteric period. It is probable that some women with prolonged periods of amenorrhea, and frequently accompanied by obesity, also belong to this category.

(4) Hyperhormonal conditions—One-third of younger women with polymenorrhea and patients of the menopausal age with menstrual irregularities have also shown excessive amounts of the anterior lobe sex factors in the blood. It is possible that this is due to a primary hyperfunction of the anterior hypophysis which results in an excessive production of ovary-stimulating substances.

My thanks are due to Mr. Pierre Lassègues for his technical services in connection with this study.

BIBLIOGRAPHY

1. Fluhmann, C. F.: Anterior pituitary hormone in the blood during pregnancy. J. A. M. A. **92**: 1744. 1929.
2. Fluhmann, C. F.: Anterior pituitary hormone in the blood of women with ovarian deficiency. J. A. M. A. **93**: 672. 1929.
3. Fluhmann, C. F.: The significance of anterior pituitary hormone in the blood of gynecologic patients. Am. J. Obst. & Gynec. **20**: 1. 1930.

4. Hofbauer, J.: Hyperplasia endometrii pituitaria. Zentralbl. f. Gynäk. **54:** 2569. 1930.
5. Fluhmann, C. F.: Hyperplasia of the endometrium and the hormones of the anterior hypophysis and the ovaries. Surg., Gynec. & Obstet. June, 1931.
6. Schroeder, R.: Der Mensuelle Genitalzyklus des Weibes und seine Störungen, Veit Stoeckel's Handbuch der Gynäkologie, Ed. 3, 1928. J. F. Bergmann, Munich.
7. Shaw, W.: Irregular uterine haemorrhage. J. Obst. & Gynaec. Brit. Emp. **36:** 1. 1929.
8. Fluhmann, C. F.: The endometrium in so-called idiopathic uterine hemorrhage. J. A. M. A. **93:** 1136. 1929.
9. Meigs, J. V.: Benign uterine bleeding, Wilfred Shaw's groups. Am. J. Obst. & Gynec. **20:** 15. 1930.
10. Smith, P. E. and E. T. Engle: Experimental evidence regarding the rôle of the anterior pituitary in the development and regulation of the genital system. Am. J. Anat. **40:** 159. 1927.
11. Zondek, B.: Hypophysenvorderlappen. Arch. f. Gynäk. **144:** 133. 1930.
12. Mazer, C. and J. Hoffman: Three hormone tests for early pregnancy. J. A. M. A. **96:** 19. 1931.

CLINICAL EXPERIENCE WITH FOLLICULAR AND HYPOPHYSEAL HORMONES

PRELIMINARY REPORT

E. C. HAMBLEN, M.D.

From the Department of Obstetrics and Gynecology,
University of Virginia Hospital
UNIVERSITY, VA.

Our knowledge of female sexual physiology has undergone marked readjustment during the past decade. Animal experimental studies have yielded newer and more scientific concepts. Using the smear test of Stockard and Papanicolaou (1), Allen (4, 5), Pratt, Doisy (2, 3), and their associates, Frank (6, 7, 8, 9) and his co-workers and others have demonstrated the physiologic activity of the follicular hormone. Evans (10, 11), Long, and their associates, Smith (12, 13, 14), and Engle (15, 16, 17), and Zondek (18, 19) and Aschheim (20, 21, 22, 23, 24) have described the sexual functions of the anterior lobe of the hypophysis. The follicular hormone has been prepared in crystalline form by Doisy (25, 26, 27, 28) and his associates. Attemps to prepare extracts of anterior hypophysis suitable for clinical trial have been reported (29, 30, 31). Various reports (32, 33, 34, 35, 36) of clinical trials of these hormones have appeared.

The purpose of this article is to report our clinical experience with active preparations of the anterior hypophyseal and follicular hormones in the treatment of various menstrual disorders in a relatively small series of patients. We have been supplied with the crystalline follicular hormone ("theelin") and with the anterior pituitary luteinizing hormone through the courtesy of Dr. E. A. Sharp (Parke, Davis & Co.). Theelin has been available in solution in 1 cc. ampules containing 40-50 Rat Units (R. U.). The anterior pituitary luteinizing hormone has been furnished in 10 cc. vials, with a potency of 50 R. U. per cc. and bearing, recently, an expiration date of short term.

The method of preparation and standardization of the luteinizing hormone has been sketched (37) briefly for us. It is prepared from the urine of pregnant women by concentration and subsequent precipitation with water-soluble, organic solvents. It is standardized on the basis of characteristic ovarian responses (APR II and APR III) in sexually immature mice.

Selection of Patients for Treatments: The patients selected for treatments were those in whom menstrual disorders were the presenting symptoms and in whom endocrinal dysfunction was the primary etiologic factor. Although the majority of these patients were of ambulant, office

type, they received complete studies with ample laboratory examinations; special diagnostic tests, including x-ray and metabolic studies, were made when indicated. The total number of patients selected for treatments was seventy; thirteen of these were unable, due chiefly to remoteness from the hospital, to take treatments regularly and, at our advice, discontinued them before any effects could be expected. Seventeen patients have only recently started treatments; the administration of the hormones in these has been too brief to warrant any conclusions being drawn. We report the results of the treatments in the remaining forty patients.

Scheme of Treatments: With the exception of several patients, to whom the vaginal pessaries incorporating the active hormone were supplied, the hormones were administered intramuscularly. When it was possible, a single hormone was used. In the majority of patients the hormones were administered daily in doses of 100 R. U. for two weeks with rest intervals of two weeks. Administration in this manner was repeated until results justified discontinuation. If it was possible, the hormones were administered during the intermenstrual phase of the cycle. Sedatives were not dispensed for the relief of subjective symptoms or combined in any way with these treatments. The only measures adjuvant to the endocrinal therapy were the correction of dietetic and hygienic errors.

Local Reactions: There were no untoward reactions at the sites of injections. In a few instances patients receiving the anterior pituitary luteinizing hormone complained of slight local pain, 24 to 48 hours after a certain injection; investigation usually revealed that the injection had been made too superficially.

Results: Brief case reports are given to detail as clearly as possible the results obtained in the treatments of the forty patients. Negative and normal physical and laboratory findings are, for the most part, omitted in these reports. Patients who are still under observation and treatment are indicated by the symbol (#).

Patients with Symptoms Referable to the Climacteric:

Case I. (#) Mrs. J. T., aged 47, para 6-5-1, came to the dispensary complaining of nervousness and headaches. During the past eighteen months her menstrual periods had gradually grown more scanty and more irregular. For the past six months she had experienced marked vasomotor instability, characterized by fainting spells, flashes, and emotional instability. General physical examination revealed nothing of particular importance. Pelvic examination showed no pelvic abnormalities. She was given theelin, 100 R. U. daily for two weeks. She noticed at the end of this treatment a disappearance of the emotional and nervous symptoms. After two weeks rest, she reported a menstrual period, which, persisting, had lasted for a week. She was given another two weeks treatment with theelin and the relief of the presenting symptoms continued. She had continued, however, to have a scant sanguinous discharge and, accordingly, was admitted to the hospital for a curettage of the uterus. The curettings were reported to show hyperplastic endometritis. Bleeding has not recurred since the operation and after two weeks of rest another series of theelin injections will be given.

Case II. Mrs. W. S. Mc., aged 53, was seen in the dispensary to which she came with the symptoms of flashes, nervousness, and vertigo since the climacteric two years previously. She also complained of a low grade lumbar backache of an inconstant character. Physical examination and pelvic examination were essentially negative. The patient was slightly under-weight. Laboratory findings were within the range of normal. She was given theelin, 100 R. U. daily for two weeks and then three times weekly for four weeks. After a week of treatment the patient was free of subjective symptoms. There was no return of menstruation.

Case III. (#) Mrs. G. G., aged 46, para 6-0-6, had had scanty and irregular menstruation for the past year. The symptoms which brought her to the gynecological clinic were extreme nervousness, loss of appetite, gaseous eructations, and an inconstant lumbar backache. Physical examination disclosed no important abnormalities. The patient was slightly under-weight. Pelvic examination revealed no pelvic disease. Laboratory findings were normal. She has been under treatment for the past six months, during which time she has received theelin, 100 R. U. three times a week for two weeks with rest intervals of two weeks. She has received relief from her symptoms, except the backache. The menstruation has become more regular but still remains scanty.

Case IV. (#) Miss L. G., aged 47, was referred to our clinic for diagnosis and treatment. She had had no menstruation for seventeen years. Her complaints were very varied and included marked emotional instability, extreme nervousness, manifested by gross tremors, and many indefinite and inconstant pains. A diagnosis of involutional psychosis was made by the neurological consultant. Her physical examination revealed nothing of consequence except marked vasomotor instability, gross tremors of extremities and exaggerated reflexes. The Wassermann test was negative. A trial of theelin was made: she was given 100 R. U. three times a week for eight weeks without any improvement or without any relief of symptoms. There was no return of menstruation.

Case VI. (#) Mrs. A. M., aged 46, was referred to our clinic with symptoms of morning parietal headaches, flashes, emotional and vasomotor instability and marked melancholia. These symptoms had appeared during the last year and had been much intensified following the cessation of menstruation seven months previously. Physical examination revealed nothing of importance except a coarse tremor, refractive error of the eyes well corrected with glasses, and a moderate obesity. Laboratory examinations were unimportant. She received theelin, 100 R. U. daily for three weeks with rest intervals of one week for three months. The subjective symptoms, except occasional slight headaches, were relieved after the first two weeks of treatment. There has been no return of menstruation.

Case VII. (#) Mrs. B. S., aged 40, para 8-2-5, was admitted to the hospital complaining of an almost constant frontal headache of approximately six months' duration. During this time there had been a marked decrease in menstrual flow, associated with extreme nervousness, flashes, emotional instability, and increased severity of the headaches. Blood pressure at time of admission was 210/160; urinalysis gave normal findings. Blood urea was 66 mgm. per 100 cc. Physical examination revealed a moderate enlargement of the heart with good regularity and no murmurs; eyes and sinuses were normal. Radiography of the sella turcica revealed a slight hypoplasia. She was given a one-fourth grain hypodermic injection of morphine at the time of admission for the immediate relief of an almost unbearable headache. Subsequent treatment consisted of a diet of moderately restricted protein and the administration of anterior pituitary luteinizing hormone, 200 R. U. daily for ten days. During this time the patient was confined to bed in the hospital. After two days of this treatment, the headache disappeared and during the last two days of the treatment there occurred the first free and normal menstrual cycle the patient had had in six months without the usual symptoms and with no headache. At the time of discharge from the hospital her blood pressure was 150/96 and blood urea was 38 mgm. per 100 cc. She is to receive further treatments.

Patients with Symptoms Referable to Artificial Menopause:

Case VIII. (#) I. R., aged 24, para 0-0-0, was referred to our dispensary for treatment of symptoms following a hysterectomy and bilateral salpingo-oophorectomy in another hospital in July, 1930. The patient complained of loss of appetite and weight, insomnia, failure to regain strength, and nervousness. Physical examination and laboratory tests revealed no abnormalities. She was given theelin, 100 R. U. daily for two weeks. She reported at the end of the

treatment a complete relief of subjective symptoms. She recently returned to the clinic after a month's rest from treatment and, during this interval, had had no return of symptoms.

Case IX. Mrs. J. G., aged 30, para 4-4-0, complained of nervousness, insomnia, flashes, and frequent attacks of vertigo. Her operative history included an operation elsewhere in 1927, at which time a left oophorectomy and right partial oophorectomy were done. She had received radium therapy elsewhere in 1928 with resulting cessation of menstruation. Her symptoms dated from that time. General examination and laboratory findings were unimportant, except for marked emotional and vasomotor instability. She received theelin, 100 R. U. daily for two weeks. There was a reduction in the severity of the symptoms and at the end of the treatment there was a noticeable improvement of vasomotor balance. She was unable to continue further treatment.

Case X. (#) E. B., aged 29, was referred to the gynecological clinic for treatment. She had had a bilateral salpingo-oophorectomy in 1919. During the past two years she had experienced flashes, vasomotor instability, characterized by nervousness, frequent sweats, and weakness, and inconstant and ill-defined headaches. Physical examination and laboratory tests disclosed no important findings. She was given theelin, 100 R. U. daily, for two weeks with relief of symptoms and disappearance of vasomotor instability. At the end of two weeks rest from treatment, she reports no return of symptoms.

Case XI. Mrs. I. K. H., aged 44, was referred to our clinic for treatment. She complained of melancholia, emotional instability, flashes, and nervous instability; these symptoms dated from radium therapy elsewhere three years previously, which resulted in the cessation of menstruation. General examination disclosed only moderate obesity. Laboratory findings were of no importance. She was given theelin, 100 R. U. daily, for three weeks. During the latter part of this treatment she began to complain of pelvic cramps, associated with a sensation of fullness in this region and discontinued treatments in fear that menstruation was returning. She received an almost complete relief of subjective symptoms; menstruation did not result from her treatments.

Case XII. Mrs. R. L., aged 45, para 6-0-6, complained of general malaise, dizzy spells and numbness in the left flank, following an operation in August, 1930, which involved bilateral salpingo-oophorectomy and supravaginal hysterectomy. General examination, pelvic examination and laboratory studies gave normal findings. She was given vaginal pessaries, each containing 50 R. U. of follicular hormone, one to be used each day. She continued this treatment for six weeks with almost complete relief of her symptoms, except the numbness in the left flank.

Case XIII. (#) E. H., aged 20, was referred to the gynecological clinic complaining of weakness, loss of appetite, pains in the muscles of the extremities and loss of weight, following an operation in December, 1930, which involved bilateral salpingo-oophorectomy. General physical examination revealed chronic infection of tonsils, malnutrition and subnormal weight. The patient was of diminutive stature. Laboratory findings were within the range of normal. She was given theelin, 100 R. U. daily, for three weeks. There was an almost complete disappearance of symptoms and she has gained five pounds.

Patients with Primary Amenorrhea:

Case XIV. (#) Miss M. H., aged 16, was seen in the gynecological clinic. She complained of delayed menarche, weakness and nervousness. General physical findings were unimportant, except that pelvic examination revealed a moderate hypoplasia of the internal genitals. She was given four series of theelin injections in daily doses of 100 R. U. for two weeks with the usual rest intervals of two weeks. Menstruation did not result. A fifth series was given with a daily dose of 100 R. U. of theelin and 100 R. U. of anterior pituitary luteinizing hormone for two weeks. Ten days following this, menstruation occurred and lasted three days. Subsequent menstrual periods have occurred: Jan. 25, Feb. 16, and March 19. The symptoms of which the patient complained were relieved with the onset of menstruation.

Case XV. Miss A. R., aged 15, complained of delayed menarche and various symptoms of vasomotor instability. General examination was normal. Pelvic examination revealed moderate hypoplasia of the internal genitalia. She was given one dozen vaginal pessaries, each containing 50 R. U. of follicular hormone, one to be used each day. At the conclusion of this treatment the patient experienced a normal menstrual flow. She did not continue treatments.

Case XVI. (#) Mrs. H. T., aged 23, was admitted to the hospital complaining of having had no menstruation. Her symptoms included pelvic cramps several days each month, absence of libido, asthenia and general weakness. Physical examination revealed moderate obesity, hypoplasia of the breasts, sparse and adolescent distribution of the pubic hair, dry skin and evidence of a moderate anemia. X-ray and metabolic findings were normal. The hemoglobin was 70 per cent; the red cell count was 3,600,000. She was given anterior pituitary luteinizing hormone daily for one week in dosage of 100 R. U. She started menstruating on the fifth day of treatment and had a normal flow of three days' duration. She has subsequently been treated in the clinic, receiving two series of anterior pituitary luteinizing hormone injections, 100 R. U. daily for ten days. The administration of iron was included in her treatment. The patient has reported four normal periods since beginning treatment. Subjective symptoms, except absence of libido, disappeared with the onset of menstruation.

Case XVII. E. M., aged 18, was admitted to the hospital for a complete study and treatment. She complained of delayed menstruation with fairly regular pelvic cramps for several days each month. Physical examination disclosed marked underdevelopment, diminutive stature, high-pitched, falsetto voice, and low I. Q. Pelvic examination showed moderate pelvic hypoplasia. X-ray, laboratory and metabolic findings were normal. She was given anterior pituitary luteinizing hormone, 100 R. U. daily, for seven days. Menstruation began on the fourth day of treatment; a normal flow resulted. She received subsequently, after discharge from the hospital, another series of the hormone treatments and a normal menstrual period occurred.

Patients with Secondary Amenorrhea:

Case XVIII. (#) Miss W. E., aged 21, was referred to the gynecological clinic complaining of marked menstrual irregularity, monthly nose bleeding, and obesity. At the time of her first visit she had had no menstruation for four months. Physical examination revealed hypertrichosis, masculine distribution of pubic hair, and moderate hypoplasia of internal genitals. X-ray and laboratory findings were normal. The basal metabolic rate was minus 15 per cent. The weight was 167 pounds. She was given anterior pituitary luteinizing hormone, 100 R. U. daily, for two weeks with rest intervals of two weeks. This treatment has been repeated twice. She has received in addition thyroid substance in daily doses of one grain. A rational obesity diet was instituted. She has experienced no nose bleeding since treatments were instituted, has had two normal menstrual periods and has lost fourteen pounds of weight.

Case XIX. (#) Mrs. I. B., aged 24, para 2-0-2, was examined in consultation for amenorrhea of one year's duration. General examination revealed no important abnormalities. Laboratory findings, and x-ray and metabolic findings were reported within the range of normal. She was given anterior pituitary luteinizing hormone, 100 R. U. daily, for two weeks. Two days following this treatment she began menstruating and continued for one week. She is now receiving a second series of treatments.

Case XX. Miss M. S., aged 21, who was seen in the gynecological clinic, complained of amenorrhea of five months' duration. Physical examination revealed an atrophic deformity of the right leg, resulting from anterior poliomyelitis ten years previously, and pelvic examination showed moderate hypoplasia of the internal genitalia. Laboratory findings were normal. She was given theelin daily in doses of 100 R. U. for two weeks. Following this treatment she experienced a menstrual period of a day's duration. She did not continue treatments.

Case XXI. (#) E. L., aged 23, complained of amenorrhea of seven months' duration. Physical examination revealed a very obese colored woman of "pituitary" type, and pelvic examination showed a congenital third degree retroversion of a hypoplastic uterus. The basal metabolic rate was minus 12 per cent. The sella turcica, from x-ray study, was reported smaller than normal. A curettage of the uterus revealed normal intermenstrual endometrium. She was given anterior pituitary luteinizing hormone in daily doses of 100 R. U. for one week. In addition she received thyroid substance daily in doses of one grain. Three weeks following the hormonal injections, menstrual bleeding began and lasted as a scant flow for five weeks. At this time the patient was admitted to the hospital and a curettage was done; microscopic study of the curettings revealed a moderate hyperplasia of the endometrium. She is now receiving a second series of anterior pituitary hormone injections.

Case XXII. (#) Mrs. P. B., aged 29, para 1-1-0, was referred to the gynecological clinic with symptoms of marked menstrual irregularity, nervousness, emotional instability and frequent frontal headaches. She gave a history of menstrual irregularity of approximately five years' duration. She had experienced varying periods of amenorrhea, one of two years, and had not menstruated for two months when she came under our care. Physical examination revealed an obese white woman with typical pituitary distribution of fat. The basal metabolic rate was minus 18 per cent. The laboratory findings were normal. The eyes, ears, nose and throat showed no abnormalities. She was given anterior pituitary luteinizing hormone in doses of 100 R. U. daily for two weeks. She was also given thyroid substance in dosage of one grain daily. A scant flow of two days' duration resulted during this treatment. She has subsequently received two series of hormonal injections with the usual rest interval. Subjective symptoms have disappeared. There has been no further menstruation. She has lost ten pounds in weight. She is still under treatment.

Case XXIII. (#) Miss E. E., aged 16, was admitted to the hospital for a complete study. She complained of absolute menstrual irregularity, since the onset of menstruation two years previously. She frequently had experienced amenorrhea of four to six months' duration. General physical findings were normal. Pelvic examination revealed a moderate hypoplasia of the internal genitalia with a small, prolapsed right cystic ovary. The uterus was curetted at this time and microscopic study showed a normal endometrium. Laboratory and x-ray findings were normal. Dates of the patient's recent menstrual periods were: December, 1929, 4 weeks; May 7, 1930, 5 days; July 12, 1930, 4 days; September 30, 1930, 4 days. She began treatments with theelin the first part of October, receiving 100 R. U., daily, for two weeks with rest intervals of two weeks. This system of treatment has continued until the present time. Since treatment was instituted the patient has had the following menstrual periods: November 2, 1930, 4 days; December 1, 1930, 4 days; January 25, 1931, 4 days.

Patients with Oligomenorrhea:

Case XXIV. (#) Mrs. M. H., aged 30, had had a hysteropexy and bilateral salpingectomy performed on our service about four months previously. At that time both ovaries were normal. Following operation she complained of marked nervousness, depression, vasomotor instability, and flashes accompanying scant regular menstrual periods. General physical findings were normal, except for moderate obesity, and the laboratory findings were normal. She was given anterior pituitary luteinizing hormone daily in doses of 100 R. U. for two weeks with rest intervals of two weeks. She has received two series of these treatments. Following these treatments, she has had two four-day periods. characterized by normal flow and without any of the subjective symptoms of which she previously complained.

Case XXV. Mrs. B. M.. aged 24, had been under our treatment for approximately two months for bilateral pyosalpingitis, receiving the usual treatment with foreign protein and douches. Her general physical examination was unimportant except that she was undernourished and slightly underweight. Laboratory findings were normal. She complained of severe menstrual pain, nervous symptoms, flashes and menstrual headaches, associated with scanty menstrual flow. She was given theelin, 100 R. U. daily for ten days. The ensuing menstrual period was of normal character and was not characterized by any of the distressing symptoms. She has not continued treatments.

Case XXVI. (#) Mrs. F. W., aged 27, para 0-0-0, was referred to our service for treatment of irregular menstruation. The symptoms included severe premenstrual backache, dysmenorrhea, scant flow, and marked mental depression during the pre- and menstrual phases. Physical examination, laboratory studies and special gynecological examinations were unimportant. She has received two series of treatments with theelin, 100 R. U. daily for twelve days with the usual rest intervals. Both ensuing menstrual periods have been regular, of normal character, and devoid of the pre- and menstrual symptoms.

Case XXVII. (#) Miss M. A., aged 22, was referred to our service for treatment. She complained of absolute menstrual irregularity since the menarche, associated with scant flow, severe premenstrual backaches, vasomotor symptoms and the presence of an urticarial rash during the pre- and menstrual phases. General physical and gynecological examinations were negative. Laboratory

findings were within the range of normal. A curettage of the uterus had been done several months previously with a report of normal endometrium. She was given theelin daily in doses of 100 R. U. for two weeks. The ensuing menstrual period was of normal character and was not associated with any of the disturbing symptoms. The skin rash did not recur.

Case XXVIII. Miss D. P., aged 15, complained of dysmenorrhea, associated with regular, but scant, menstrual periods of two to three days' duration. Physical examination and laboratory studies revealed nothing abnormal, except a moderate hypoplasia of the internal genitals. She received two series of theelin in daily doses of 100 R. U. for two weeks with rest intervals of two weeks. She had two normal menstrual periods following these treatments; there was no pain of any severity and each period lasted three to four days.

Case XXIX. Miss L. T., aged 21, came to our clinic with a complaint of menstrual irregularity associated with scanty flow. The chief complaint was the premenstrual and menstrual pains. Physical examination was negative except for moderate hypoplasia of the internal genital organs. She was given theelin in daily doses of 100 R. U. for three weeks. At the conclusion of this treatment there was a normal menstrual period of four days' duration without the usual associated pains. The patient was unable to continue treatments.

Case XXX. Miss D. Q., aged 20, complained of dysmenorrhea and scanty irregular menstruation. She had had a hysteropexy six months previously without relief of these symptoms. General physical examination and laboratory studies were unimportant. She was given theelin daily in doses of 100 R. U. for two weeks. The ensuing menstrual period was almost entirely free from pain, except for a few hours during the first day, and the period lasted four days, being characterized by a normal flow. She was unable to continue treatments.

Case XXXI. (#) Mrs. C. E., aged 23, para 3-1-2, was referred to the gynecological clinic for treatment. Her symptoms included weakness, nervousness, constipation, loss of libido and loss of appetite. Her menstruation had been absolutely irregular since the menarche and the menstrual flow had always been very scanty and lasted two to three days. General physical and pelvic examinations revealed no abnormalities. The laboratory findings were not significant. She received three series of injections of theelin in doses of 100 R. U. daily for two weeks with rest intervals of two weeks. She has just completed the third series of injections. Two menstrual periods have occurred since treatments began. One period lasted from February 5 to 10; the other lasted from March 7 to 14. Both periods were quite normal and not characterized by the usual symptoms. The patient's general health has improved with the establishment of normal, regular menstruation.

Patients with Idiopathic Menorrhagia:

Cases XXXII, XXXIII, XXXIV, XXXV included four patients with idiopathic menorrhagias, who were treated with daily doses of theelin (100 R. U.) for from four to six weeks without any influence of the excessive menstruation.

Case XXXVI. (#) Mrs. D. B., aged 19, was admitted to the hospital complaining of marked menstrual irregularity, characterized by intervals of amenorrhea followed by periods of menorrhagia. At the time of admission the patient had had a scant flow for two and one-half months. She had experienced menstrual irregularity since her menarche and had had radium therapy twice elsewhere. General physical examination, laboratory and x-ray studies were negative. The basal metabolic rate was normal. The patient was given a thorough curettage: microscopic study of the scrapings showed evidence of chronic endometritis with slight fibrosis. She was then given the following treatment: rest in bed: theelin in doses of 100 R. U. daily for twelve days; and calcium lactate, 120 grains daily (38). After the fourth day of this treatment, bleeding ceased. A communication from this patient six months after discharge from the hospital reports that for the first three months her menstrual periods were quite irregular and scanty, but that her last three menstrual periods have been regular and lasted four to five days.

Case XXXVII. Miss I. A., aged 22, was admitted to the hospital for treatment of excessive menstruation. Her history revealed that her menstruation started at the age of twelve and was very irregular. At the age of thir-

teen, she was given radium by an attending physician. There followed an amenorrhea of about six months and since that time the patient has experienced very irregular menstrual periods. Her immediate history included a normal menstrual period, August 10, 1930, followed by the resumption of bleeding on August 30, 1930, which continued very profuse for seven days, at which time the patient was admitted to the hospital. General physical examination, laboratory findings and metabolic studies were essentially negative. Pelvic examination revealed a small hypoplastic uterus in midposition. Curettage was done at this time and showed the evidence of considerable fibrosis. She was given theelin, 100 R. U. daily for twelve days. At the conclusion of this treatment she had another uterine hemorrhage and was again admitted to the hospital. She received another vigorous curettage of the uterus and was then given parathormone and calcium lactate as in Case XXXVI. Bleeding ceased on the fifth day of treatment. She was discharged from the hospital two days later, but was treated in the office for one week with daily injections of 100 R. U. of theelin. Ten days later she experienced a normal menstrual period of five days' duration. She has subsequently had four other regular, normal menstrual periods.

Patients with Hyperemesis Gravidarum:

Cases XXXVIII, XXXIX, XL include three patients with hyperemesis gravidarum. The entire three had failed to respond to the usual treatments with rectal bromides, glucose infusions and hypodermoclyses and dietetic regimes. These measures had been tried in all three cases at least one week and, despite no food or fluids being given by mouth, the patients continued to vomit. One patient received 200 R. U. theelin daily for three days; another received 500 R. U. of theelin during three days; the other received 400 R. U. of theelin during two days. All three of these patients ceased vomiting. One of these patients returned to the hospital three weeks after treatment with an incomplete abortion.

Summary of Results of Treatments:

1. Patients with symptoms associated with menopause (natural or artificial): (A) Relief of subjective symptoms: excellent, 8; good, 4 (treatments were inadequate in two); no relief, 1. (B) Effect on menstruation: none, 10; menorrhagia, 1; increased regularity, 2. There was no recurrence in patients in whom menstruation had ceased.

2. Patients with amenorrhea (primary and secondary): (A) Relief of associated symptoms: Excellent, 7; good, 3. (B) Effect on menstruation: menstruation initiated, 4; menstruation recurred, 5; no effect, 1.

3. Patients with oligomenorrhea: (A) Relief of symptoms: excellent, 4; good, 4 (treatment inadequate in two). (B) Effect on menstruation: menstruation was more regular and the menstrual flow of a more normal character in all cases.

4. Patients with idiopathic menorrhagia: No effect on menorrhagia, 4; excellent return to normal, 2 (both cases treated with parathormone and calcium lactate in addition to hormone).

5. Patients with hyperemesis gravidarum: Vomiting ceased, 3; one case returned after three weeks with an incomplete abortion.

Comments: We are aware that this small number of patients does not warrant any general conclusions. The period of observation in many instances has been insufficient. None of these patients has been observed longer than six months.

The well-known psychological factors that characterize treatment of patients with symptoms associated with menstrual disorders are borne in mind and the possibility of spontaneous remissions in the severity of these symptoms (39) is appreciated. These factors must be considered even in attempts to interpret improvements in the menstrual cycle.

A thorough and scientific study of the clinical effects of these hormones on large series of carefully selected patients should be made. Adequate dosage should be determined; the possible duration of treatments should be investigated. The character of the bleeding which results following the administration of these hormones must be investigated with a view of determining whether it be physiologic or not. Our studies are to be continued with these facts in mind.

SUMMARY

1. The results of treatments of forty patients with theelin and anterior pituitary hormones are reported; thyroid substance was used, in addition, in three patients.

2. Thirteen patients with symptoms associated with the menopause (natural or artificial) were treated. The relief of subjective symptoms was excellent in eight patients and good in four. One patient received no benefit. There was no effect on menstruation in 10 cases; menorrhagia developed in one patient; menstruation became more regular in two patients.

3. Ten patients with amenorrhea (primary and secondary) were treated. The relief of associated symptoms was excellent in seven; good relief was obtained in three. Menstruation was initiated in the four patients of the primary type of amenorrhea; menstruation recurred in five of the six patients with secondary amenorrhea.

4. Eight patients with oligomenorrhea were treated. The relief of the associated symptoms was excellent in four and good in the remaining four. In all cases menstruation became more regular and the flow was of a more normal type.

5. Six patients with idiopathic menorrhagia were treated. In four there was no benefit; in the two in which parathormone and calcium lactate were used in addition to theelin the results were excellent.

6. Three patients with hyperemesis gravidarum were treated. Vomiting ceased in these cases. One patient returned after three weeks with an incomplete abortion.

BIBLIOGRAPHY

1. Stockard, C. R. and G. N. Papanicolaou: The existence of a typical oestrus cycle in the guinea-pig: with a study of its histological and psychological changes. Am. J. Anat. **22**: 225. 1917.
2. Allen, E. and E. A. Doisy: An ovarian hormone; preliminary report on its localization, extraction and partial purification, and action in test animals. J. A. M. A. **81**: 819. 1923.
3. Doisy, E. A., E. Allen and J. P. Pratt: Ovarian follicular hormone; its distribution in human genital tissues. J. A. M. A. **85**: 399. 1925.

4. Pratt, J. P. and E. Allen: Clinical tests of the ovarian follicular hormone. J. A. M. A. **86:** 1964. 1926.

5. Allen, E., J. P. Pratt, Q. U. Newell and L. J. Bland: Hormonal content of human ovarian tissues. Am. J. Physiol. **92:** 127. 1930.

6. Frank, R. T. and M. A. Goldberger: Female sex hormone; its occurrence in the circulating and menstrual blood of human females; preliminary report. J. A. M. A. **86:** 1686. 1926.

7. Frank, R. T. and M. A. Goldberger: Female sex hormone; demonstration of female sex hormone in human blood; technique; clinical applicability. J. A. M. A. **87:** 1719. 1926.

8. Frank, R. T.: The Female Sex Hormone, 1929, Charles C. Thomas, Springfield, Ill.

9. Frank, R. T., H. M. Kingery and R. G. Gustavson: Female sex hormone; analysis of factors producing puberty. J. A. M. A. **85:** 1558. 1925.

10. Evans, H. M. and J. A. Long: Characteristic effects upon growth, oestrus and ovulation induced by the intraperitoneal administration of fresh anterior hypophyseal substance. Proc. Med. Acad. Sc. **8:** 38. 1922.

11. Evans, H. M. and M. E. Simpson: Comparison of anterior hypophyseal implants from normal and gonadectomized animals with reference to their capacity to stimulate immature ovary. Am. J. Physiol. **89:** 375. 1929.

12. Smith, P. E.: The disabilities caused by hypophysectomy and their repair; the tuberal syndrome in the rat. J. A. M. A. **88:** 158. 1927.

13. Smith, P. E.: Hastening development of female genital system by daily homoplastic pituitary transplants. Proc. Soc. Exper. Biol. & Med. **24:** 131. 1926.

14. Smith, P. E.: The induction of precocious sexual maturity by pituitary homeotransplants. Am. J. Physiol. **80:** 114. 1927.

15. Smith, P. E. and E. T. Engle: Induction of precocious sexual maturity in the mouse by daily pituitary homeo and heterotransplants. Proc. Soc. Exper. Biol. & Med. **24:** 561. 1927.

16. Smith, P. E. and E. T. Engle: Experimental evidence regarding rôle of anterior pituitary in development and regulation of genital system. Am. J. Anat. **40:** 159. 1927.

17. Smith, P. E. and E. T. Engle: Precocious sexual maturity in the mouse following pituitary transplants. Anat. Rec. **35:** 22. 1927.

18. Zondek, B.: Das Hormon des Ovariums und des Hypophysenvorderlappens. Med. Klin. **23:** 463. 1927.

19. Zondek, B. and S. Aschheim: Hypophysenvorderlappenhormon und Ovarialhormon im Harn von Schwangeren. Klin. Wchnschr. **6:** 1322. 1927.

20. Zondek, B. and S. Aschheim: Hypophysenvorderlappen und Ovarium. Beziehungen der endokrinen Drüsen zur Ovarialfunktion. Arch. f. Gynäk. **130:** 1. 1927.

21. Zondek, B. and S. Aschheim: Schwangerschaftsdiagnose aus dem Harn. Klin. Wchnschr. **7:** 8. 1928.

22. Zondek, B.: Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons; Grundlagen und Technik der Methode. Klin. Wchnschr. **7:** 1404. 1928.

23. Zondek, B. and S. Aschheim: Ovulation in der Gravidität, ausgelöst durch Hypophysenvorderlappenhormon. Endokrinologie, **1:** 10. 1928.

24. Zondek, B.: Weibliche Sexualhormon. Klin. Wchnschr. **7:** 946. 1928.

25. Doisy, E. A., S. Thayer and C. D. Veler: Abst., Am. J. Physiol. **90:** 329. 1929.

26. Doisy, E. A., S. Thayer and C. D. Veler: Crystals of follicular hormone. Proc. Soc. Exper. Biol. & Med. **27:** 417. 1930.

27. Doisy, E. A., S. Thayer and C. D. Veler: Preparation of crystalline ovarian hormone from urine of pregnant women. J. Biol. Chem. **86:** 499. 1930.

28. Veler, C. D., S. Thayer and E. A. Doisy: Preparation of crystalline follicular hormone; theelin. J. Biol. Chem. **87:** 357. 1930.

29. Zondek, B.: Weitere Untersuchungen zur Darstellung, Biologie und Klinik des Hypophysenvorderlappenhormons (Prolan). Klin. Wchnschr. **8:** 157. 1929.

30. Ibid. Zentralbl. f. Gynäk. **53.** 834. 1929.

31. Falta, W. and F. Högler: Über das Hypophysenvorderlappenhormon. Klin. Wchnschr. **9:** 1807. 1930.

32. Sevringhaus, E. L. and J. S. Evans: Clinical observations on the use of an ovarian hormone: Amniotin: Am. J. M. Sc. **178:** 638. 1929.

33. Dodds, E. C. and J. D. Robertson: Clinical experiments with estrin. Lancet, **1:** 1390. 1930.

34. McClendon, J. F., G. Burr and F. F. Wildebrush: Induction of menstruation in women by use of ovarian hormone. Proc. Soc. Exper. Biol. & Med. **26:** 430. 1929.

35. Campbell, A. D. and J. D. Collip: On the clinical use of the ovary-stimulating hormone of the placenta. Canad. M. A. J. **22:** 219. 1930.

36. Zondek, B.: Weitere Untersuchungen zur Darstellung, Biologie und Klinik des Hypophysenvorderlappenhormons (Prolan). Ztschr. f. Geburtsh. u. Gynäk. **95:** 361. 1929.

37. Sharp, E. A.: Personal communication.

38. Allen, E. and H. C. Goldthorpe: A study in the use of Parathormone in the control of menstrual bleeding. Am. J. Obst. and Gynec. **17:** 344. 1929.

39. King, J. T. and E. Patterson: Observations on the menopause. II. The effects of various ovarian preparations on symptoms of the menopause and on basal metabolism. J. A. M. A. **91:** 1453. 1928.

THE USE OF LIQUOR FOLLICULI IN OBSTETRIC VETERINARIAN PRACTICE*

GIACOMO PIGHINI
Director of the Scientific Laboratories of the Psychiatric Institute
REGGIO EMILIA
AND
STEFANO RIVABELLA
Director of the Veterinarian Surgical Clinic of the Royal Veterinarian Institute
PARMA, ITALY

In this Journal one of us [Pighini in collaboration with Colonna (1)] hinted at the possible utility of systematic endocrinology in veterinary obstetrical practice. After noting the prompt expulsion of a mummified foetus of a cow injected with liquor folliculi, we decided to study experimentally the value of such treatment in all those cases in which it was possible to surmise that an exciting and normalizing stimulation of the genital tract might modify functions altered either through congenital hypoplasia or pathological processes.

The therapeutic indications for sexual hormonization are based on the latest findings of the experimental physiologists in this field. To avoid repetitions on the subject (2, 3) we shall recall only the points which are of immediate practical interest.

Experimental physiology has showed several modifications brought into the female organism by the sexual hormone—modifications which occur normally before and during the estrual cycle and which by overdosage can be exaggerated. Such modifications are of a great interest in the clinic since, on the one hand, they throw light upon the pathogenesis of many morbid conditions of the genital tract as well as upon some abnormalities of the individual constitution and, on the other hand, offer us a therapeutic means to combat successfully these and other genito-sexual alterations brought about by occasional diseases.

The sexual hormone (especially the active principles found in the liquor folliculi) acts only when administered parenterally. The rupture of the follicle, pouring its hormone into the peritoneal cavity, shows the elective way of absorption in the normal organism. Therefore by treating female animals with injections—hypodermic, endomuscular or intraperitoneal—of liquor folliculi (or of its extracts) several modifications are induced in the sexual organs, be the animals castrated or not.

(a) The vaginal epithelium, normally constituted of two strata, basal and superficial, hypertrophies; the basal elements enter in karyokinesis and form layers of pavement epithelium; the superficial elements become swollen and exfoliate—in the rodents they become horny—so that within

*The data of this paper have also been published in Italian in "La Clinica Veterinaria," 1929.

the vagina are found epithelial cells with and without nuclei [horny (Schollen)]. The leukocytes disappear. These findings in the rodents in the laboratories—as shown by Stockard and Papanicolau, Allen and Doisy, etc.—render it possible to follow "in vivo" the structual modifications in their successive steps.

(b) In the uterus the cells of the mucosa begin to secrete, become swollen and full of mucin; karyokinesis takes place; the epithelium of the cornua becomes stratified and forms many glandular crypts; the other glands also undergo a conspicuous development. By carrying the treatment to the epithelial reaction stage a muscular reaction can be produced with proliferation of fibres and a hypertrophy, which may become 3-4 times the normal thickness. The vessels are swollen and full of blood. All these modifications are similar to those brought about by the estruation, and by intensifying the treatment (stimulation) a striking similarity is reached with the post-estrual period and the beginning of pregnancy.

(c) In the mamma the areola becomes congested; the glandular acini hypertrophy and increase in number and size; the organ grows larger.

(d) The primordial folliculi of the ovary rapidly develop and ripen; their atresia quickly follows with a consequent increase of the interstitial elements.

From this complex of histological changes brought about by the injection of liquor folliculi we are justified in concluding that its sexual hormone is, in itself, sufficient to determine the physiological estrual phases and the development of the secondary sexual characteristics. The estrual phenomena due to the direct action of this hormone may be summed up as: congestion of the whole genital tract—uterus and vagina—increase of the uterine and vaginal mucous secretion, hypertrophy and hyperplasia of the uterine muscular tissue, decidual reaction in the elements of the stroma and, finally, glandular hyperplasia of the mammae.

The active, specific hormone of the liquor follicularis being thus found it became obviously desirable to investigate its utility in the medical clinic, either to follow in its several phases the pathogenesis of some disease of the sexual organs or to attempt its cure. In the human clinic quite a number of therapeutic attempts have been made (Watrin, Novak, Fellner, Brouha and Simonnet, Laquer, Zondek and Braun, Allen, Hirst, Massazza, Serdukoff, Pighini, Vitali, Mazza, etc.); cases of uterine infantilism with consequent sterility, cases of amenorrhea and dysmenorrhea, of acid leukorrhea, of hemorrhagic metritis, of sexual frigidity, of climacteric disorders—such as arthropathies, etc.—were treated with success by follicular therapy. One of us had a great use of it in studying the pathogenesis and treating opotherapically several nervous and mental diseases connected with alterations in the sexual field [Pighini (4)]. In this way a practical demonstration was obtained of the value of the extracts directly taken from liquor folliculi and placenta, as compared with several commercial ovarian preparations. These latter upon biological test did not show any specific

action (Fellner, Loewe). It is now easy to understand why with the ovarian preparations earlier used hardly any result was obtained; and why some few results were had with preparations taken from the corpus luteum, especially in menopause. Yet if the corpus luteum, besides some not well known principles of its own, contains the sexual hormone (Frank) in a greater concentration than the rest of the ovary, deprived of liquor folliculi, the liquor folliculi is a thousand-fold richer in hormone, as has been proved with comparative doses. Therefore the greatest concentrations of "rat units," the best physio-therapeutic effects are obtainable from preparations of liquor folliculi or of placenta, which also shows a great amount of active principle.

Of course the pharmaceutical houses were not slow in throwing the new hormonal product onto the market, following the remarkable experimental studies of Allen and Doisy, of Laquer, Zondek, etc., who showed the several ways of extracting the active principle of the liquor as well as of the placenta (of late Zondek has even extracted it from the urine of pregnant women). Thus we have the various "Folliculines" (Liquor folliculi, D. I. F. Co.; glandofoline, Richter; follicular hormone, Squibb; Estrogen, Parke, Davis & Co.; Thelykinine, etc.) and some preparation from the placenta, as the very good preparation, Menformon, of Laquer, prepared by the firm of Degewop of Berlin.

All these preparations really contain the sexual hormone assayed in "rat" or "mouse" units and are a great deal more active than the so-called "whole ovary preparations." Yet such an activity does not stand comparison with the natural product of the liquor taken directly from the ripe graafian follicles. The lower value, perhaps, is due to the fact that in the process of extraction with lipoid solvents now used the peroxides of the lipoids damage the active principle, or it may be due to other substances contained in the original liquor (co-hormones, co-enzymes) which enhance the activity of the specific hormonal principle. Some investigators who have had the chance of experimenting on many subjects in medical and gynecological practice prefer (as Fellner of Vienna and Serdukoff of Moscow) the product freshly prepared directly either from the placenta or from the liquor folliculi.

One of us (Pighini) who tried the activities of the several fractionated extracts of the liquor folliculi, came to the conclusion that the liquor "in toto" is the most active on large animals and on man (2, 3). Therefore he prepared a stable product of liquor folliculi, taking it aseptically from the ovarian follicules of the cow or mare and treating it with carbolic acid (1 cc. of 4 per cent solution of phenol for 10 cc. of liquor). A small amount of globulins is precipitated and through centrifugation a limpid liquid is obtained that is golden yellow, sterile and of a lasting hormonal activity.

The "Estrofollicolina fenicata," as it is called, is put in ampoules of 3 cc. and is even more active than the plain folliculine. The addition of

the phenol seems to enhance its activity, as has also been demonstrated by Ferni (6) to be true as regards his vaccins and serovaccins with 1 per cent of phenol. The small amount of phenol (0.012 per ampoule of 3 cc.) cannot be toxic. Each cubic centimeter of the "estrofollicolina fenicata" has the activity of 3-5 "rat" units, but when injected into large animals it shows an activity much greater than that demonstrable in mice or rats.

While for these rodents 1 cc. of one of the best commercial preparations, "Menformon," contains 40 mouse units, the same dose injected into mammals (sow, cow, mare, woman) is a great deal less active than 1 cc. of our "estrofollicolina fenicata," which, in turn, for the rat is eight times less potent. That is due to the fact that the cyclic sexual functions differ among different classes of animals. The mammals mentioned are extremely sensitive to the genuine product of the graafian follicle containing all the hormonal physiological principles, while the same mammals show a weaker reaction to the lipoid or aqueous extracts, which again are very active on the rodents. While at least 1 cc. (injected in fractional doses in two days) of our folliculina is needed to obtain hypertrophy of the uterus in the white rat, 6-8 cc. in the same time suffice to arouse the uterine activity in the cow, an animal four to five thousand times heavier. In the same way woman is extremely sensitive to even small doses of natural folliculine: at times a single injection of 2-3 cc. has sufficed to bring about a very prompt modification of the vaginal mucosa, to stop the acid leucorrhoeic secretion and to start the structual changes. We shall see what a successful application can be made of a product fractionally extracted and deproteinized—such as never was obtained from commercial preparations.

Knowing the relations of functional interdependence between the thyroid and the ovary (Biedl, Kranter, Kocher, Curschmann, Knauss, Lendberg, etc.) and the ripening action on the folliculi through small doses of thyroid extract [Pighini and DePaoli (7)], which substance in greater amount has a degenerative action and provokes abortion in pregnant animals [Mosbacher, Knauss, Pighini (8)] Pighini thought of associating the thyroid extract with the follicular liquor, to see whether its potency could not be increased. Therefore he started experiments, adding to the "estrofollicolina fenicata" very small doses of the "endotiroidina" of the Istituto Sieroterapico Milanese, using one ampoule of it with 20 cc. of liquor.

The slight thyroidization gave to the estrual secretion a more energetic action on the uterus and on the vagina. Owing to this result we (also following in this Pende's conception on pluriglandular treatment) made quite a number of experiments with the "estrofollicolina tiroidizzata." (It is prepared by the "Laboratory Farmacologico Reggiano" in Correggio.)

The fight against the several diseases of the female genital organs of the domestic animals—especially of the cow—arouses more than any other subject the interest of the veterinarian practitioner: it is enough to think

of their influence on sterility and abortion to understand its importance. On the other hand, when we confront the difficulties to be met in the treatment of such diseases and even more of the sterility of the domestic animals—from the economic standpoint—we realize the importance of the problem and the necessity of trying every means to succeed.

While surgery and sera have been used in both prophylactic treatment of utero-ovarian lesions and curative treatment of sterility, be it functional or with an antomo-pathological substratum—opotherapy is yet in its beginning; and the sexual hormonization, which has hardly gained a foothold in the human clinic has thus far had very few applications in veterinary medicine.

Thus far opotherapy has been used to provoke estruation, availing ourselves of the most obvious characteristic of the sexual hormone. The follicular liquor, so far as we know, has been used only by the Americans, Murphey, McNutt, Zupp and Aitrens (9) and Rulffes (10) to correct the functional sterility of cows and provoke parturition. The American authors aspirate the "liquor," filter it through asbestos or a Berkefeld candle, and inject it intravenously, using for one dose the amount that can be extracted from one ovary. Rulffes also takes the liquor directly from the ovary of a sow or cow, treats it with tricreosol 0.5 per cent and injects it hypodermically, 30-40 cc. at a time. In several cases the first quoted author obtained estruation after a daily injection over periods of from 6 to 25 days. Rulffes, with larger dosage, obtained the reaction after only one hypodermic injection (two cows and three heifers, after two injections in two cows and one heifer, after three injections in three adult cows and a heifer). One cow failed to react to these doses.

Dolder brought on estruation in cows by using sterile extracts of whole ovary (11); a similar product was used by Becker to restore the impaired ovarian function in a case of sterility with anaphrodisia; and Frei and Staheli with massage of the ovary and hypodermatic or endomuscular graft of ovary (12). There is a case of expulsion of a dead foetus of a cow quoted by Zupp and Murphey. A triple dose of corpus luteum (one corpus luteum corresponds to one dose) had been previously injected to avoid uterine contraction; three weeks later six doses of estrual hormone were injected. In the meantime at rectal examination a mummified foetus was found surrounded by a gelatinous mass. The corpus luteum was enucleated and two days after the gelatinous mass came out and later the foetus also. As one can see the treatment was rather complex (13). A clean-cut result was the one quoted by Pighini and Colonna (1) in which 3 cc. of "estrofollicolina fenicata" was enough to provoke the expulsion of a mummified foetus in three days.

Our clinical application of "liquor folliculi" in the veterinarian obstetrical and gynecological field has now extended to many subjects—nearly all cows—showing the most diverse alterations of the sexual apparatus and accompanied by sterility. In many cases only "estrofollicolina

fenicata'' was used; in several others this with the addition of thyroid. This latter treatment was used in cases in which stimulation of the ovarian and uterine activity was needed. Massive injections were never used, but successive ones of 3 cc. daily or every two or three days until the effect was obtained (of late we have even used ampoules of 5 cc.). Finally, we realized that the promptest result was reached by three or four successive injections, one every twelve hours. The injection was always made hypodermically in the lateral region of the neck. We chose this rather than the intravenous route since absorption is slower and the organism hence provided for a longer time with the follicular hormone. There has not occurred any local irritation or any unfavorable general reaction. The cases will be discussed in several groups.

Group I consisted of young females not yet in estruation in spite of having reached the puberal age: the injection was made to bring them to sexual maturity through a hormonal influence.

Group II comprised puberal females not in estruation, owing to hypofunction of the ovary.

The subjects of these two groups present the form of sterility which the American authors call functional, where no lesion of the genital apparatus can be detected through rectal and vaginal examination.

Group III is made up of animals with retention of the placenta either owing to interstitial cotyledonitis or uterine atony. In some of the subjects the injection of liquor was used instead of manual extraction of the placenta; in some cases the manual extraction had been tried unsuccessfully on account of inflammatory adhesions; in others the injection was used as adjunctive to manual extraction, to excite the functional activity of the uterus and its involution, which processes are often abnormal in these cases in which the inflammatory process diminishes the contractile energy of the uterus.

Group IV composed animals with chronic catarrhal or purulent endomethritis from previous puerperal inflammation.

Group V was made up of cows with retention of dead foetuses.

We shall sum up the clinical histories of the several groups.

First Group—First Case: A sow 9 months old weighing 90 kgm., had apparently never been in rut; copulation did not result in pregnancy, and the usual aphrodisiacs were without effect. On November 9th a hypodermic injection of 3 cc. of "estrofollicolina fenicata" was made in the auricular region. Four days after there was a full manifestation of estruation, and at the first cohabitation she became pregnant and was normally delivered.

Cases 2-3-4-5: Young cows, 2 years old, of the bruno-alpine race, were in splendid condition of nutrition. They had never been in rut, but no alteration of the genital apparatus can be detected through rectal and vaginal examination. Two of them received three ampoules of estrofollicolina fenicata and the two others, four, *i.e.*, one ampoule daily. Rut appeared in all in from three to five days after the last injection. Pregnancy followed copulation and proceeded normally.

Cases 6-7-8-9-10: Young cows of mixed Svitto-parmigiana breed, 22-24 months old, were in good condition of nutrition with no lesions of the genital apparatus, but they had failed to come into rut. Two to three injections of estro-follicolina were made in daily succession. In four to five days after the last injection rut occurred with fecund intercourse.

Second Group—Cases 1-2: Two mares, 8 years old, in the service of Dr. Vet. Candisi, had failed to come into rut, but after two injections of estrofollicolina estruation occurred, followed by pregnancy.

Cases 3-4: Two mares, 7-8 years old (Dr. Vet. Cav. Vecchia) had not been in rut for several years. After three injections pregnancy was secured.

Case 5: A Reggian cow (Dr. Vet. Vezzani) had been 20 months without rut. Two injections of liquor folliculi were given, followed by estruation and pregnancy.

Third Group—Case 1: A Swiss cow, 4 years old (Dr. Vet. Orlandini) retained the placenta after normal delivery of the foetus. Examination, 6 days after delivery, revealed a rather bad general condition with sepsis; there was a fetid dark discharge from the vulva, the cervix was open and the uterus tender and atonic, in subinvolution. The treatment was simply one injection of "estra-follicolina with thyroid" every twelve hours. After the third injection complete expulsion of the placenta and amniotic sac occurred and the uterine tone was re-established. Rapid general betterment followed and in a few days normal health was regained.

Case 2: (Dr. Vet. Vecchia.) The foetus of a cow had been expelled March 6, 1929; on March 11th the placenta was still retained. After 3 cc. of "estro-follicolina tirodizzatta" cramps occurred but not expulsion. On March 15th a second injection was given and 24 hours later complete expulsion of the placenta and amniotic sac was obtained. The milk secretion, which had been very scanty before, quickly increased.

Case 3: A Swiss cow, 3 years old (Dr. Vet. Trombini) had had a seven-months' abortion with retention of the placenta. The fifth day after an injection of two ampoules of "liquor tiroidizzato" slight cramps started. The injection was repeated two days later and after 48 hours complete expulsion of placenta and involucra took place.

Case 4: A Swiss cow, 9 years old, suffered premature delivery, retention of placenta and uterine atony. Three days after a first injection of liquor was followed by a second, 12 hours later. In two days expulsion of the involucra and placenta took place and a normal puerperium and increase of milk secretion followed.

Case 5: A cow 6 years old had a seventh month abortion with retention of the placenta. Two days after the abortion two ampoules of liquor folliculi were injected. Intense cramps followed and 36 hours later there was complete expulsion of the placenta and involucra. The cramps kept on two days more, but without apparent trouble to the animal.

Case 6: A cow 5 years old had a seventh month abortion with retention of the placenta. An injection of liquor folliculi two days after the abortion was followed in 30 hours by complete expulsion of placenta and involucra. Increase of milk secretion occurred. These last three cases have been under Dr. Trombini's treatment.

Case 7: A Belgian mare, 6 years old, was taken to the Veterinarian Surgical Clinic of Farma for delivery. This occurred on Feb. 13th, with slow labor. Twelve hours after delivery the placenta was still retained and there was no uterine tonus. After one injection of "follicolina tiroidizzata" complete expulsion of placenta occurred within a few hours. A normal puerperium followed.

Cases 9-10-11-12: Five Swiss cows from 7 to 9 years old had normal deliveries, but retention of the placenta. In the stables of their owners in the years before there was found a severe form of epizootic abortion; as regards the abortion a cure has been obtained with indicated treatments and vaccinations. At this time all the cows were being delivered at term, but often retention of the placenta was observed. This is anything but unusual in the stables where Bang's disease is found. We ourselves had the opportunity of finding this symptom as the only manifestation of that disease, as shown with the biologic proof. In all these cases the placenta was extracted manually on from the fourth to the seventh days. We found the cervix almost always well open, the uterus dilated and atonic and full of ichorous secretion: two cows presented a rather severe general sepsis. The manual extraction did not thoroughly succeed in all

cases, but we only try to clean as well as possible by sponging the foul discharge. The treatment was completed with injections of liquor folliculi, one ampoule every day until the puerperium became normal; at the most, five injections were given. The general condition of the animals improved very promptly and the uterus regained its tonus. Afterwards the cows were brought to the male and four became pregnant; the pregnancy ran a normal course.

Fourth Group—Cases 1-2-3: Three Swiss cows, two 4, one 9 years old, were all delivered about two months before, with difficult labor but regular expulsion of placenta. They had not rutted. Their general condition bad, the nutrition poor. From the vulva there was a dense, purulent discharge, while upon rectal exploration the uterus appeared larger than normal, with thick walls and tender to examination. A daily injection of "estrofollicolina tiroidizzata" was given for four successive days. The vulvar discharge increased, estruation became manifest in from 10 to 12 days and then again 22 days after, at which period all became pregnant. The general condition through the usual treatments quickly improved.

Cases 4-5: Two Swiss cows, 5 to 6 years old, had been ill four months with chronic endomethritis; they showed estruation, but remained sterile. After five injections of liquor, one every other day, the animals became pregnant.

Case 6: (Dr. Vet. Vezzani.) A cow 6 years old of Reggian stock showed chronic catarrhal endomethritis following abortion; there had been no rut for the preceding year. A daily injection of estrofollicolina for three days brought on estruation with copious discharge from the vulva ten days after the treatment.

Fifth Group—Case 1: (Dr. Vet. Moretti.) A cow 3 years old, of Reggian stock, nine months after breeding presented ichorous discharge from the vulva, bad general condition, anorexia, absence of rumination, tympanism and fever. The cervical canal allowed only two fingers to pass. Upon rectal examination a dead fœtus was found which appeared emphysematous. There were no expulsive pains. Two injections of liquor folliculi were given, one every twelve hours, which brought on labor pains and within twelve hours the cow was delivered of a dead foetus with intact membranes. Rapid improvement followed.

Case 2: (Dr. Vet. Moretti.) A Metis cow, 6 years old, was found at the eighth month to have in the uterine horn a mummified foetus. Two ampoules of liquor folliculi were injected and in four days labor began and the foetus was expelled.

As shown by the foregoing cases, the specific hormonal treatment has been applied to the most different processes which may interest the veterinarian obstetrician; and, though, as regards some groups, the cases are not many, yet the results obtained through the use of liquor folliculi were such as to make us believe that this preparation will have a great success in obstetrical therapy.

Our experiments emphasize the great activity of the follicular hormone in initiating rut in young animals as well as in adults that had not been in rut for a long time. Compared with aphrodisiac products the "estrofollicolina fenicata" appeared innocuous to the organism and constant in its effect, at least for all the cases due to ovarian hypofunction. Where, though, its action was really invaluable, was in cases of retention of the placenta, inflammatory processes of the uterus and retention of dead foetuses.

It seems superfluous to talk of the importance of these affections and of all the remedies and treatments hitherto tried in this field. Such therapy as has previously been used has often failed on account of uterine inertia and also on account of the peculiar structure of the uterine sac in these animals, so that even slight lesions may become worse and chronic

with the harmful consequences, we all know [Bernardini, Ghisleni, Tagliavioi, etc. (14-15-16)].

We only state that the "liquor folliculi" when compared with the best known therapy (manual extraction of the placenta, mixtures intended to soften the cotyledons, antiseptic powders either concentrated or diluted and the oxytocic means like Metrodina's, Gynergen's and ours often used with good result) shows undeniable advantages, due to its peculiar principles, demonstrated by the latest result of experimental physiology in the field of the sexual hormonization. Its action is not that of an ecbolic, the best of which may provoke uterine contractions very different from normal. The liquor folliculi has essentially a physiological action; and if in any kind of therapy—uterine more than any—we must never forget the "primum non nocere," the follicular hormone absolutely corresponds to the demand, as it tends to normalize the altered genital tract.

Even with the most constant ecbolic, local and general bad effects are anything but unusual (strong, dangerous cramps, interruption of rumination, diminishing of milk secretion, etc.) and their importance is patent especially when it comes to milch cows. Nothing of the kind ever occurred in our cases treated with liquor folliculi.

The organism fights with its own means stimulated through the hormonal action; and as in normal estruation we obtain through the follicular hormone histological changes in the genital field, similar changes are obtained with "estrofollicolina." The uterus in rut hypertrophies becomes hyperemic, and the cellular strata of its mucosa undergo karyokinesis, forming numbers of glandular sacs. Anybody who knows—even superficially—the anatomo-pathologic substratum of the endomethritic lesions, will see at once the importance of these autochthonous formative processes tending to give back to the viscus its anatomo-functional integrity, therefore putting it in the best condition to recover from the pathologic process. While with our usual sterilizing agents we act on the surface, or with the usual oxytocics we provoke uterine contractions, which may even render conditions worse by tetanizing the uterus and preventing its emptying, with the specific hormonal treatment a reaction is awakened from the inside outward, which returns the tissue in the best normal conditions to defend itself against the infection and bring back the organ to normality.

As a fact in all our cases of retention of the placenta, of catarrhal endomethritis with pus and septic absorption, fever, severely bad general condition, we saw a quick awakening of the dormant energies of the genital tract, its prompt coming back to normal by expelling the uterine content, resolution of the septic process and return to health. Seeing the reintegrative properties of the liquor folliculi on the musoca of the genital tract and therefore also of the vagina, in which it provokes active epithelial stratification, it is our intention to apply the new hormonal treatment in cases of granulous vaginitis.

SUMMARY

In obstetrical veterinarian practice animals were injected with follicular extract or with this in combination with thyroid and phenol ("estrofollicolina tiroidizzata e fenicata"). Good results were obtained in:

(1) Ten females which had never before been in rut;

(2) Five females for a long period without estruation;

(3) Twelve females with retention of the placenta;

(4) Six affected with chronic, catarrhal purulent endomethritis;

(5) Two females with retention of dead foetuses.

The treatment with the estrofollicolina is a valuable means in obstetric veterinarian practice for all these cases, and especially for cases of endouterine inflammatory processes, to fight which the most rational therapeutic means often have hitherto been ineffective.

BIBLIOGRAPHY

1. Pighini, G. and A. Colonna: This Journal, **13**: 393. 1929.
2. Pighini, G.: Biochim. e. terap. sper. **16**: 577. 1929.
3. Pighini, G.: Biochim. e. terap. sper. **17**: 1. 1930.
4. Pighini, G.: Riv. sper. di freniat. **53**: 1. 1929.
5. Serdukoff: Gynec. et Obst. **19**: 39. 1929.
6. Fermi, C.: Policlinico (sez. prat.) **36**: 155. 1929.
7. Pighini, G. and M. de Paola: Biochim. e. terap. sep. **7**: 4. 1925.
8. Pighini, G.: Policlinico (sez. med.) **32**: 334. 1925.
9. Murphey, H. S., G. W. McNutt, B. A. Zupp and W. A. Aitrens: J. Am. Vet. M. A **68**: 443. 1926.
10. Ruffles: Cited by G. Gerosa e A. Mirri in "La sterilitá negli animali domestici," Milano, 1929.
11. Dolder, E.: Schweig. Archiv. fur. Tirthrilk, **68**: 1926.
12. Frei, W. Stahell: Deutsche thierarztliche Wchnschr. 1926.
13. Zupp, B. A. and H. S. Murphey: Vet. Med. **21**: 261. 1926.
14. Bernardini: Clin. vet. **40**: 331. 1917.
15. Chisleni: "Il moderno Zooiatro." 1913.
16. Tagliavini, A.: Clin. vet. **50**: 75. 1927.

MULTIPLE ADRENAL TRANSPLANTS AND PREMATURE SEX DEVELOPMENT IN FEMALE WHITE RATS

A PRELIMINARY REPORT

L. B. NICE AND A. L. SHIFFER
From the Department of Physiology, Ohio State University
COLUMBUS

In a series of multiple adrenal gland transplants into immature female white rats, we have been testing whether early sex development will occur following this operation.

Method: The procedure employed consisted of transplanting six adrenal glands from young adult white rats, nine to ten months old, into the dorsal muscles of immature females, ranging from 16 to 23 days of age. These transplants were made under light ether anaesthesia. Three glands were sutured into the muscles on the left and three on the right side. In all cases the glands were transected before being transplanted. The time the vaginal canal opened, as used by Long and Evans (1) was taken as the indication of sexual development.

Results: Thus far we have had ten rats to survive this operation and kept under observation. These are recorded in Table I.

TABLE I

Number of Rat	Born	Adrenal Transplants	Vaginal Canal Opened	Days After Transplants When Canal Opened	Age of Rat When Canal Opened
1	April 20, 1931	May 7, 1931	May 13	6 days	23 days
2	April 20, 1931	May 7, 1931	May 18	11 days	28 days
3	April 20, 1931	May 7, 1931	May 15	8 days	25 days
4	April 22, 1931	May 12, 1931	May 29	17 days	37 days
5	April 22, 1931	May 12, 1931	May 28	16 days	36 days
6	April 28, 1931	May 19, 1931	June 4	16 days	37 days
7	April 28, 1931	May 21, 1931	June 4	14 days	37 days
8	May 10, 1931	May 26, 1931	June 5	10 days	26 days
9	May 10, 1931	May 26, 1931	June 5	10 days	26 days
10	May 10, 1931	May 28, 1931	June 3	6 days	24 days

Our results are too few to make anything but a preliminary report, yet they are significant in showing that early sex development did occur in six of our ten rats at ages below the normal for such development. These results are quite similar to those of other workers with anterior pituitary transplants (2).

The earliest age we have had the vaginal canals open in a large series of normal female rats in this laboratory was 29 days, with 10 rats, with an average of 34.47 days for 249 animals, as found by Kraft (1931) (3). Long and Evans (1) give a range between 34 and 109 days, with an average of 72 days. Our complete series of these adrenal transplant animals which are under way will be reported in the near future.

We are indebted to J. L. Friedman and A. L. Simons for assistance in these experiments.

SUMMARY

1. Early sex development as shown by the opening of the vaginal canal occurred in six of ten rats which survived multiple adrenal transplants.

2. The vaginal canals opened 6, 8, 10, and 11 days after the transplants were made, while the rats ranged between 23 and 28 days of age.

BIBLIOGRAPHY

1. Long, J. A., and H. A. Evans. 1922. Memoirs of the University of California. Vol. 6.
2. Evans, H. M., and J. A. Long. 1921. Anat. Rec. **21**: 62; Smith, P. E., and E. T. Engle, 1927. Amer. Jour. Anat. **40**: 159; Zondek, B., and S. Aschheim. 1927. Klin. Woch., **6**: 248; Ibid. 1928, **7**: 831. Kraft, Ruth M. 1931, unpublished results.
3. Kraft, Ruth M. 1931. Unpublished results from this laboratory.

EFFECTS OF ESTROGENIC SUBSTANCES AND THE LUTEINIZING FACTOR ON PREGNANCY IN THE ALBINO RAT

LOUIS LEVIN, PHILIP A. KATZMAN AND EDWARD A. DOISY
From the Laboratory of Biological Chemistry,
St. Louis University School of Medicine
ST. LOUIS

Investigations of the effect of estrogenic substances on pregnancy have not led to uniform, well-defined results. Since all of the previous work has been carried on with crude preparations, the explanation of the differences may lie in the nature of the impurities. The isolation of the two crystalline estrogenic compounds, theelin and theelol, afforded us the opportunity of excluding the effects of extraneous substances.

Brouha and Simonnet (1) in 1925 reported that extracts of liquor folliculi, administered to rats during late pregnancy, had no effect on the gestation.

In contrast to this work, Parkes and Bellerby (2) in 1926 found that in the white mouse pregnancy could be interrupted and rapid return to oestrus be brought about by administration of oestrin. Small dosages were used (one to five mouse units), although during the later stages of pregnancy larger quantities were necessary in order to bring about abortion. Later (1930) Parkes (3) reported that oestrin alone, in doses as high as 380 M.U. did not regularly cause abortion in the white mouse. However, he found that if a small dose of the oxytocic pituitary principle, which when administered alone does not cause abortion, is given immediately after the last oestrin injection, quite regularly abortion occurs several hours after the injection of oxytocin.

Zondek and Aschheim (11), treating mice with folliculin during the second half of pregnancy, noted no adverse effect on the pregnancy, using dosages up to 10 mouse units. However, increased dosages regularly produced abortion.

Smith (4), in agreement with the work of Parkes and Bellerby (2), found that injection of extracts of follicular fluid (one to forty rat units) during the first five days of pregnancy, effectively terminated the pregnancy and brought about rapid return to oestrus in the albino rat.

The work of Gostimirovic (5) in part agreed with that of Parkes and Bellerby (2) and that of Smith (4). He reported that mice, treated with folliculin-menformone before and immediately following copulation, showed a very low percentage of fecundity as compared with normal untreated animals. However, if treated with folliculin-menformone during the second half of pregnancy, mice showed no deviation from untreated pregnant mice.

Kelly (6) also agrees with the above mentioned investigators. Working with guinea pigs, he found that oestrin, injected immediately after copulation, invariably prevented conception. He reported that in the guinea pig pregnancy can be terminated at any stage, the amount of oestrin necessary to bring about the termination increasing as pregnancy proceeds.

Kelly (7) also reported that anterior pituitary extracts did not prevent conception in guinea pigs, although juice of fresh glands caused death of the animal in a number of cases. Both fresh glands and the pituitary principle from urine caused abortion if administered during the later stages of pregnancy.

Engle and Mermod (8) in 1928 found that transplantation of fresh anterior pituitary into pregnant rats and mice prevented implantation and led to resorption or expulsion of the fetus. Pregnancies were interrupted less often in the later than in the earlier stages.

Teel (9) reported that treatment with hypophyseal growth hormone during the last week of pregnancy, prolonged the pregnancy for two or three days.

Evans and Simpson (10) found that administration of anterior hypophyseal sex-maturity hormone gave a prolongation of pregnancy similar to that noted by Teel (9).

EXPERIMENTAL

Having at hand the crystalline estrogenic compounds, theelin and theelol, and also purified ovary-stimulating extracts from the urine of pregnant women, it seemed advisable to determine the effect of these substances on pregnant animals. Effects of such estrogenic and luteinizing substances may be studied from two viewpoints. First, prevention of implantation of fetuses, and second, interruption of pregnancy after implantation has occurred. For the present, we have chosen to study the latter point, since evidence may be obtained more easily from such a study. Our data must not be construed as offering any evidence concerning the prevention of implantation.

Sexually mature albino rats were used as experimental animals. Copulation was determined by the presence of sperm in the vaginal smear, which was taken daily throughout the experiment. The day after the finding of sperm was taken as the first day of pregnancy. The animals were never treated until the appearance of the placental sign, which was taken as the ultimate indication as to whether the animal was pregnant. It was found that of the 78 copulations observed, only 57 (or 73 per cent) proved to be fertile and resulted in pregnancy of the animal. To obtain additional evidence regarding the progress of the pregnancy, the animals were weighed every day throughout the experiment.

The theelin and theelol used were pure crystalline preparations from the urine of pregnant women and were of known potency and purity (12).

(13). These were usually injected in the form of weak alkaline solutions, although in the case of the small doses, dilute alcoholic solutions were used.

The ovary-stimulating substance from the urine of pregnant women was prepared in this laboratory by an unpublished method. The preparations were assayed on mice. Therefore, the amounts of this substance used are reported in mouse units. One mouse unit is that amount which, administered subcutaneously in six injections over a period of three days to nineteen-day-old female mice, causes opening of the vagina, with concurrent oestrus, on the twenty-second to twenty-fourth day of age. The preparations used varied in concentration from 300 to 1000 mouse units per cubic centimeter with a potency of 50 to 500 mouse units per milligram.

Control animals were injected with isotonic saline solution.

All injections were made subcutaneously and were usually divided into three injections per day, extending over a period of from one to three days, except for a few cases in which the injections extended over a longer period. The maximum amount of solution injected per day was three cubic centimeters.

Some difficulty was experienced in a few cases, in that the mothers either ate the litters a few days after parturition or refused to care for the young. This, when it occurred, was usually in the case of first litters.

Twenty-one pregnant rats were injected with theelin in doses varying from 20 to 600 rat units. The injections were made at various times during the second half of pregnancy as shown in Table I. Of these, twenty

TABLE I

EFFECT OF THEELIN ON PREGNANCY OF RAT.

Rat	Day of Injection	Total R. U. Injected	Day of Parturition	Number in Litter	
2	13–14	20	21	10	
5	12–13	20	21	6	
11	13–14	20	23	7	
12	12–13	20	22	9	
15	12–13	20	21	9	
19	13–14	20	21	9	
21	12–13	20	22	8	
90	14–15–16	230	21	6	
99	14–15–16	400	21	9	
100	13–14–15	400	22	5	
85	15–16–17	500	21	6	
92	14–15–16	540	21	9	
95	15–16–17	540	22	4	
97	13–14–15	540	21	10	
80	17–18	600	21	7	All eaten in first 5 days.
81	16–17	600	..	..	Autopsied on 27th day. One monstrous deformed fetus.
82	17–18	600	21	8	
83	17–18	600	22	9	
87	12–13–14	600	22	4	
94	15–16–17	600	22	5	
98	14–15–16	600	22	9	

resulted in normal pregnancy, parturition and litter. One litter was eaten during the first five days after delivery, but this was later found to occur each time this rat delivered a litter. The one abnormal pregnancy, rat 81, persisted until the autopsy was performed on the 27th day. One fetus, very large and much deformed, was found in utero.

Twenty-two pregnant rats were injected with theelol, dosages varying from 75 to 500 immature rat units or 22 to 150 spayed rat units (13). The injections were made between the 13th and 16th days of pregnancy as shown in Table II. Twenty of the twenty-two treated animals pro-

TABLE II

EFFECT OF THEELOL ON PREGNANCY OF RAT.

Rat	Day of Injection	Total R. U. (Immat.) Injected	Total R. U. (Spayed) Injected	Day of Parturition	Number in Litter	
9	16	75	22	22	9	
39	16	150	45	22	6	
32	16	225	68	24	4	All dead when found. 2 in utero.
37	16	225	68	22	8	
38	16	225	68	21	10	
41	16–17	300	90	21	9	
44	14–15	300	90	22	6	All eaten in first two days.
8	17–18	450	135	22	10	8 dead when found.
65	15–16	450	135	22	7	
66	15–16	450	135	21	9	
67	16	450	135	21	7	
71	16	450	135	..	..	Died on 21st day. 7 fetuses in utero.
75	16	450	135	22	7	
77	15	450	135	23	2	
78	13–14	450	135	21	9	
79	16	450	135	22	4	
64	16–17	500	150	21	7	All killed and mangled in first week.
69	16–17	500	150	21	10	
70	16–17	500	150	23	8	5 dead when found. Mangled and chewed.
72	16–17	500	150	22	5	
74	16–17	500	150	23	9	All dead in two days. Starved (?).
76	16–17	500	150	21	7	Killed and eaten in first week.

ceeded to normal parturition, although in five of these cases the litters were eaten or killed within the first week after delivery. One rat died on the 20th day. Autopsy revealed apparently normal fetuses in utero. There were seven old corpora lutea in the ovaries, the number in each ovary corresponding to the number of fetuses in that horn of the uterus. The remaining rat, number 32, delivered four young on the 24th day, but all were dead when found. Autopsy of the mother revealed two more fetuses in utero. Eight large corpora lutea and several small ones were observed in the ovaries.

In none of the animals treated with theelin or theelol did oestrus occur, as indicated by a positive smear, at any time after the injection until after the litters had been removed, usually at the age of three weeks.

Eight pregnant rats were injected with the extracts of the ovary-stimulating substance from the urine of pregnant women. Dosages varied from 1500 to 7000 M.U. Injections were made at various stages of late pregnancy (14th to 21st day) as shown in Table III. Of the eight animals treated with these extracts, none resulted in normal parturition. In each case, except one, parturition was delayed, the extent of delay not being known, since in these cases autopsy was performed in order to observe effects on the genital tracts. In each case, partial resorption of some of the fetuses had occurred, although in one case (rat number 101) some of the fetuses were still alive when removed from the uterus. This indicates that the extracts did not exert their effect through toxicity. Also,

TABLE III

EFFECT OF OVARY-STIMULATING SUBSTANCE FROM URINE OF PREGNANT WOMEN.

Rat	Days of Injection	Total M. U. Injected	Number of Injections	Day of Autopsy	
68	14 to 21 (incl.)	7000	16	27	2 fetuses in utero. Partial resorption. Many corpora lutea.
73	16 to 22 (incl.)	6160	14	28	9 fetuses in utero. Partial resorption. Many corpora lutea.
88	17–18–19	2000	7	..	Litter of 6 delivered on 20th day. 5 dead when found. Other dead next morning.
91	14–15–16	2100	7	26	8 fetuses in utero. Partial resorption. Fetuses abnormal size. Many corpora lutea.
93	17–18–19	1800	6	23	Loss in weight before autopsy. 1 fetus in utero. Partially resorbed. Apparantly aborted from other horn. Corpora lutea not as numerous as in other cases.
96	15–16–17	2700	8	26	6 fetuses in utero. Partial resorption. Many corpora lutea.
101	17–18–19	2000	6	24	9 fetuses in utero. 4 alive, 5 dead. 2 partially resorbed. Many corpora lutea.
102	18–19–20	1500	6	26	1 young delivered on 23rd day. At autopsy 7 fetuses in utero. Very much resorbed. 1 fetus almost to vagina. Several follicles. Many corpora lutea.

the fetuses were usually of normal or abnormal size, indicating that development had not been inhibited. Each autopsy revealed ovaries studded with corpora lutea, in most cases too numerous to count. Also, several large follicles were usually observed.

The one pregnancy which was not delayed (rat number 88) resulted in the delivery of six young on the 20th day. Five of the young were dead when found and the sixth died the next night.

Nine animals were injected with isotonic saline, the amount administered varying from 2 to 6 cc. All proceeded to normal parturition, as shown in Table IV. In one case, however, the litter died within two days after delivery.

TABLE IV

CONTROLS.

Rat	Day of Injection	Total Injected cc.	Day of Parturition	Number in Litter	
10	12–13	2	22	7	
13	14–15	2	21	9	
14	13–14	2	21	10	
17	12–13	2	21	5	
29	12–13	2	22	10	
36	12–13	2	22	9	
25	16–17	3	21	9	
26	16–17	3	22	8	
4	17–18	6	22	10	All dead in two days.

DISCUSSION

From the above results it appears that if administered as solutions of the crystalline compounds during the second half of pregnancy neither theelin nor theelol affects the pregnancy adversely. This is in agreement with the work of Brouha and Simonnet (1) and the Gostimirovic (5). Explanation of the disagreement of this work with that of Parkes and Bellerby (2), (Smith (4) and Kelly (6) offers opportunity for specula-

tion. Toxicity of the preparations used may be one factor influencing the results. The extracts used by Miss Smith were apparently very crude, one rat unit weighing from five to ten milligrams. Kelly (6) reports that large dosages of the preparation he used, when injected during the second half of pregnancy, in most cases resulted in maternal as well as fetal death. Moreover, it is to be noted that these preparations injected into males and non-pregnant females proved toxic in many cases, causing death of the animal. Thus we see that perhaps toxicity of material used may mask the results obtained.

Also it may be true, as Gostimirovic (5) suggests, that the amount of solution injected and not the number of units is the determining factor in bringing about abortion. However, this is highly problematical and more evidence is needed on this point.

The ovary-stimulating substance from the urine of pregnant women, however, seems to prevent parturition in some way. Pregnancy is noticeably prolonged, similarly to the prolongation described by Teel (9), and by Evans and Simpson (10). These investigators probably used different substances, obtained by different methods or from different sources. That the extract used by the authors had a powerful luteinizing effect on the ovaries of the treated animals is obvious even from the limited number of experiments carried out. In every case, ovarian examination at autopsy revealed an abnormal number of large corpora lutea. In almost all cases, the ovaries were fairly studded with the corpora lutea, which appeared to constitute by far the greatest part of the bulk of the ovary. The preparation appears to function like the luteinizing principle of the anterior hypophysis which was used by Evans and Simpson (10).

The results obtained here, as well as those of Evans and Simpson, are difficult to correlate with those of Engle and Mermod, who were able to cause abortion by transplantation of anterior hypophyseal tissue into pregnant rats and mice. Perhaps as Evans and Simpson suggest, transplantation stimulates the follicular apparatus causing the liberation of follicular hormone and so keeps the birth mechanism in a normal state or even stimulates it. This is also the explanation given by Engle and Mermod.

However, the ovary-stimulating preparations used in the experiments reported here were known to be free of theelin or theelol. If, as is apparently believed by some investigators, parturition is due to degeneration of the corpus luteum of pregnancy and the rise of the follicle which ovulates immediately post-partum, then the mechanism of this luteinizing substance in preventing parturition is easily explained. The secretion of the great numbers of corpora lutea overrides the secretion of the rising follicle and so parturition is prevented.

However, this view cannot be easily correlated with the idea of antagonism between the luteal and follicular hormones. Enormous quantities of theelin or theelol which, according to this concept of hormone antag-

onism, should terminate pregnancy, did not alter the course of the gestation in any way. However, our information seems to be too incomplete to warrant a coherent explanation of the observations.

SUMMARY

The administration of crystalline theelin or theelol to the albino rat during the second half of pregnancy has no detectable effect on the length of the gestation period or the survival of the litter.

The ovary-stimulating substance from the urine of pregnant women, administered to the albino rat during the second half of pregnancy, delays or prevents parturition.

Large dosages of theelin, theelol or the ovary-stimulating substance from the urine of pregnant women, when administered to pregnant ablino rats, fail to produce estrus as indicated by the vaginal smear technique.

BIBLIOGRAPHY

1. Brouha, L. and H. Simonnet: Compt. rend. Soc. de Biol. **93:** 557. 1925.
2. Parkes, A. S. and C. W. Bellerby: J. Physiol. **62:** 145. 1926.
3. Parkes, A. S.: J. Physiol. **69:** 463. 1930.
4. Smith, Margaret G.: Johns Hopkins Hosp. Bull. **39:** 203. 1926.
5. Gostimirovic, D.: Biol. Zentralbl. **50:** 599. 1930.
6. Kelly, L. G.: Surg., Gynec. & Obst. **52:** 713. 1931.
7. Kelly, L. G.: Anat. Rec. (supplement) **48:** 50. 1931.
8. Engle, E. T. and D. Mermod: Am. J. Physiol. **85:** 518. 1928.
9. Teel, H. M.: Am. J. Physiol. **79:** 170. 1926.
10. Evans, H. M. and M. E. Simpson: Proc. Soc. Exper. Biol. and Med. **26:** 595. 1929.
11. Zondek, B. and S. Aschheim: Endokrinologie, **1:** 10. 1928.
12. Kahnt, L. C. and E. A. Doisy: This Journal, **12:** 760. 1928.
13. Curtis, J. M. and E. A. Doisy: J. Biol. Chem. **91:** 647. 1931.

SEX HORMONES IN THE BLOOD SERUM OF MARES

III. SOME CHEMICAL PROPERTIES OF THE OVARY-STIMULATING PRINCIPLE

HAROLD GOSS AND H. H. COLE
College of Agriculture, University of California
DAVIS

The blood serum of the pregnant mare has been found to contain large amounts of an ovary-stimulating substance (Cole and Hart, 1). We have some evidence that the urine of pregnant mares is relatively free of this factor.* It has been demonstrated that in the human the ovary-stimulating substance is more concentrated in the urine than in the blood serum. These facts suggested the possibility that the substances from the two sources, producing an apparently similar biological reaction in the rat, might be different in chemical or physical composition. Evidence has been obtained by Collip (2) which indicates that the ovary-stimulating material prepared from placenta may not be identical with the hormone in the urine of pregnant women.

In the present investigation, an attempt has been made to determine some of the chemical properties of the ovary-stimulating factor present in mare serum during pregnancy. In this paper we have designated as the ovary-stimulating principle, from whatever its source, that factor which stimulates follicle development and produces luteinization in the ovaries of immature female rats after subcutaneous injection. The evidence at hand is still too insufficient to venture a statement regarding the number of hormones concerned in these reactions.

It may be well to review briefly some of the chemical and biological properties of gonad stimulating substances derived from different sources.

Zondek and Aschheim (4), and Zondek (5) have determined some of the chemical properties of the gonad-stimulating substance removed from the urine of pregnant women. They have found that it is damaged by heating to 60° C. and destroyed by boiling. It is easily destroyed by strong acids and alkalis, easily dialyzed, insoluble in ether, is adsorbed by charcoal, and precipitated by alcohol. Administered orally it may be active by increasing the dose as little as 10-15 times that necessary to produce a reaction by subcutaneous injection. These authors have reported two gonad-stimulating hormones in the urine of pregnant women, although they have been unable to show any chemical differences in the two substances (Prolan A and B). Dickens (6) has substantiated and enlarged upon some of the above findings. He has found that the hormone passes only very slowly through parchment but more rapidly through collodion; is effective orally when 40 R. U. are given; is destroyed slowly by pepsin and trypsin, and is precipitated by ammonium sulfate, colloidal iron, and tannic acid. Further, he gives the reaction to several color tests. Reiss, Schäffner, and Haurowitz (7) have shown that the hormone from the urine of pregnant women is inactivated by trypsin only after activation of the trypsin with enterokinase.

*In eight instances we took blood and urine samples coincidentally. Each sample was tested for its content of ovary-stimulating hormone. All of the samples were taken between the 40th and 75th days of pregnancy when large amounts of the hormone are present in the blood serum. In only two of the eight cases was the hormone demonstrated in the urine and in these the concentration was low. In one instance there were approximately 100 R.U. per cc. of the hormone in the serum while 10 cc. of the urine gave a negative reaction. This is not in accord with the data presented by Zondek (3), in which he shows a relatively small difference between the hormone content of the blood and that of the urine of pregnant mares.

Reichert, *et al.* (8), found that if the hypophyses were removed from rats the Prolan had no effect showing that the gonadal effect of Prolan is dependent upon an intact hypophysis. Evans, Meyer and Simpson (9) have further evidence indicating that the substance present in Frolan, an extract of the urine of pregnancy, is a hormone activator rather than a hormone.

Very little has been done with the chemical properties of the gonad-stimulating substance in the anterior hypophysis. Fevold, Hisaw, and Leonard (10) have recently shown that inactive and active fractions may be prepared from the hypophysis and when these fractions are mixed the reaction is greatly increased. Claus (11) has prepared a crystalline substance from the desiccated anterior hypophysis which has a gonad-stimulating effect. It would appear, because of the drastic chemical treatment employed, that the substance procured cannot be identical with the active fraction found in the urine of pregnancy.

Collip (2, 12, 13) has studied the chemical properties of a gonad-stimulating substance of placental origin. His active material will withstand boiling in dilute acetic acid and it is soluble in alcohol. The oral dose is very little more than the subcutaneous dose.

In view of the recent paper by Evans, Meyer and Simpson, one might venture the supposition that Claus (11), and Collip (2, 12, 13) were dealing with the gonad-stimulating hormone, whereas Zondek (5), and Dickens (6) were concerned with the activator of the hormone.

There is a wealth of literature dealing with the general biological considerations in regard to the gonad-stimulating hormone. Smith and Dortzbach (14) found that the growth hormone appeared in the anterior hypophysis of the pig foetus in detectable amounts some little time before the gonad-stimulating hormone could be recognized. The body growth hormone appeared when the foetus had attained a crown-rump length of 9-11 cm., whereas the gonad-stimulating hormone did not appear until a crown-rump length of 17-18 cm. had been attained. Considerable study has been made of the amounts of the gonad-stimulating substance present in the anterior pituitary at different phases of the reproductive period. Also quantitative relationships of the hormone depending upon sex and the presence or absence of the gonads have been determined. Smith and Engle (15) have been able to show that hypophyses of guinea pigs removed during dioestrum contained more of the gonad-stimulating hormone than did those removed when the vaginae were open. Evans and Simpson (16) found very little difference in the amount of gonad-stimulating hormone of the hypophyses of pregnant and non-pregnant rats and cows. Phillip (17) found that the amount of gonad-stimulating hormones present in the human hypophysis is greater in the non-pregnant than in the pregnant individual. This has been confirmed by Zondek (5). These species differences may be explained tentatively by a difference in the functional state of the human hypophysis as compared to that of the rat and cow during pregnancy. Evans and Simpson (18) have found the hypophyses of male rats about doubly effective as those of the female in regard to their gonad-stimulating properties. This also may possibly be explained by the degree of function depending on sex. It has been shown by Engle (19) and confirmed by Evans and Simpson (20) that the hypophyses of gonadectomized animals contain greater quantities of the gonad-stimulating hormone than do those from normal animals. This apparently cannot be explained by assuming that the hypophysis of the gonadectomized animal has reduced its activity, for Zondek (21) has found that the amount of gonad-stimulating hormones in the urine of women is increased following castration.

Zondek (22) has found further that there is an increased amount of hormone present in the urine in certain pathological conditions such as genital carcinoma. This was first shown by Aschheim and Zondek (23) at the time of their description of the pregnancy test. It should be mentioned that Zondek (24) has an improved technique for the diagnosis of pregnancy.

Studies upon the histolcgical changes in the anterior hypophysis at various times of the reproductive period have been made by Baniecki (25), Charipper and Haterius (26), Nelson (27), and others.

It is almost impossible to compare the type of reactions produced by substances of different origin because of the fact that the amount administered and the methods of administration have been variable and uncertain. In fact, several papers have appeared which make it apparent that both the method of administration and the amount administered have an important bearing upon the reaction obtained. For example, Evans and Simpson (28) showed that subcutaneous injection was more effective than intraperitoneal. Further, Friedman (29) found that a single intravenous injection of urine of pregnancy was sufficient to produce ovulation in the mature rabbit, whereas neither transplanted anterior hypophyses

nor the intraperitoneal injection of urine of pregnancy produced a similar effect. Engle and Smith (30) found that the length of time between implantations had an effect upon the type of reaction. The latest report of Engle (31) would make it appear that the reaction obtained by hypophyseal implants is very similar to that obtained by injection of urine of pregnancy. However, Evans and Simpson (32) have pointed out that if one doubles the dose by the implant method the ovarian reaction is approximately double, whereas they did not find the same to be true for the injection of urine. The reactions obtained by Collip (2) using an extract of the placenta upon mature non-pregnant and pregnant rats do not correspond to those reported by Smith and Engle (33), Engle and Mermod (34), and Kelly (35) using hypophyseal implants or to those secured by Zondek (5), or Kelly (35) with extracts of urine of pregnant women. It is surprising that Collip's extract has such a pronounced effect upon the ovaries of immature rats and yet does not upset the rhythm of the oestrous cycle of the mature female in this species.

The evidence at hand indicates that the gonad-stimulating substance affects the ovaries of female mammals and to a lesser extent the testes of males; the accessory reproductive organs of the male are stimulated more than the testes, However, this same relationship apparently does not hold for birds and cold-blooded animals. Riddle (36) has shown that the reproductive organs of male ring doves are affected to a greater extent than those of the female. Burns and Buyse (37) likewise showed that the administration of anterior hypophysis had a marked effect upon the testes of salamander larvae (Amblystoma tigrinum) with very little effect upon the ovaries. Zondek (5) had negative findings after transplanting hypophyses of frogs (Rana esculenta) into rats and mice.

It is not possible to determine on a weight basis the dose sufficient to produce an ovarian reaction in different species. Zondek (38) reports that a smaller dose is needed for the rat than for the mouse and that the dose of the rabbit is about 30 times that of the rat dose. Further, the dose for the human is about 60 rat units. We have found that the minimal dose for the pig is surprisingly small.

Mason and Wolfe (39) have found that the hypophyses of rats on vitamin A-deficient diet have a greater power to induce sexual maturity than those on control diets. This would indicate a loss of functional activity for several authors have evidence that storage of the hormone in the hypophysis is associated with decreased function.

The effect of oestrin upon the hypophysis has been investigated by Meyer, Leonard, Hisaw and Martin (40). They found that the injection of oestrin into rats reduced the stimulating effect of their hypophyses. This might be interpreted as evidence for the hypothesis that oestrin has a stimulating effect upon the anterior pituitary.

That the hypophysis plays a rôle in ovulation is shown by the experiments of Fee and Parkes (41), and Deanesly, Fee, and Parkes (42). When the hypophysis was removed one hour after copulation ovulation was inhibited but if the operation was performed later than one hour after copulation ovulation occurred.

MATERIAL AND METHODS OF TESTING THE PREPARATIONS

Blood was drawn from mares in early pregnancy, that is between the 56th and 132nd days. The blood was allowed to clot, the serum removed and stored at 32° to 34° C. We have found that the ovary-stimulating substance is not appreciably affected when serum is stored for a year at the temperature indicated. In every instance, the serum was tested for potency just prior to chemical treatment.

Immature female rats, twenty-one days old, were used to test the various fractions. The material was usually given in a single injection and graded doses of each fraction were given to 3-6 rats. The increase in the size of the ovaries, determined by weighing the dissected ovary to the nearest mgm. and the histological character of the ovaries were the criteria used in determining the potency of the fraction. The ovaries were

weighed with bursae and oviducts attached in order that the search for tubal ova might be facilitated. In a large number of cases, the ovaries were sectioned serially and a study made of the character of the stimulated ovary. When the ovarian development was not sufficiently marked to be recognized by weight alone, serial sections were made to determine if one or more follicles had developed or become luteinized. In addition to this, vaginal smears were made at the time of autopsy and the uteri dissected and weighed.

We did not attempt to make close distinctions between the potencies of the various fractions. This would involve the use of large numbers of rats for each test and would appear to be impracticable until more data concerning the chemical properties had been obtained. Some of the results of the animal tests made upon the various fractions are summarized in Table I.

TABLE I

THE EFFECT OF CHEMICAL TREATMENT UPON THE POTENCY OF THE OVARY-STIMULATING FACTOR IN BLOOD SERUM

Fraction Tested	No. of Rats Used	Average Dose	Body Weight	Weight of Ovaries	Weight of Uterus	Vaginal Smear Reaction
		cc.	gms.	mgm.	mgm.	
a. The effect of concentrating the serum						
Serum concentrated to ⅓ original volume at 36°	6	0.17	52	46	130	+
Untreated serum (control)	6	0.17	52	67	147	+
b. Filtration through a collodion membrane						
Filtrate as it passed through membrane	3	8.0	48	21	27	—
Residue made up to same concentration as original serum	3	5.0	53	164	122	+
Untreated serum (control)	3	5.0	47	120	125	+
c. Dialysis of blood serum						
Dialysate after 8 hours	2	7.0	57	23	23	—
Residue not dialyzing	3	1.7	50	91	162	+
Untreated serum (control)	5	1.6	48	38	107	+
d. The fractional precipitation of blood serum with Na_2SO_4						
Precipitate salted out by 14% Na_2SO_4	2	15.	46	20	21	—
Precipitate salted out between 14 and 17%	2	15.	55	31	177	+
Precipitate salted out between 17 and 22%	2	15.	41	62	116	+
Precipitate salted out between 22% and saturation	2	15.	44	29	172	+
Filtrate saturated with Na_2SO_4	2	30.	48	18	22	—
Untreated serum (control)	2	15.	44	64	179	+
e. Effect of heating Na_2SO_4 precipitate						
Precipitate salted out between 17 and 22% heated 30 min. at 60° C	3	2.1	61	57	123	+
Untreated precipitate (control)	6	2.1	50	51	124	+
f. Treatment of blood serum with pepsin and trypsin						
Serum treated with pepsin and dialyzed, pH 6	2	2.0	54	78	185	+
Serum treated with pepsin pH 6 and then trypsin pH 7	2	2.0	60	29	61	+
Dialysate of serum treated with pepsin	3	4.6	47	22	24	—
Untreated serum (control)	3	1.7	50	91	162	+
g. Treatment of blood serum with pepsin and trypsin (2nd experiment)						
Serum treated with pepsin at pH 2-3, and dialyzed	4	7.0	50	26	23	—
Dialysate from above	3	3.0	38	15	23	—
Serum treated with trypsin alone at pH 7 and dialyzed	3	3.0	54	21	24	—
Dialysate of serum after trypsin digestion	3	3.0	41	16	25	—
Untreated serum (control)	3	3.0	44	114	191	+

EXPERIMENTAL

A. Effect of Concentration of Serum at Low Temperature

A sample of active serum was concentrated at 36° C., under a pressure of 30 mm. mercury, to 1/3 of its original volume. After dilution with saline to the original volume, this treated serum when injected had a potency similar to the untreated serum.

B. Effect of Ultrafiltration of Serum

Ultrafiltration was next applied. A sample of serum was placed in a collodion bag ultrafilter and held under a pressure of 145 mm. Hg. for 12 hours. At the end of this time the volume of the filtrate was 3/5 of the original volume of the serum. On dilution with saline to the original volume of serum, the residue in the sack was as potent as before treatment, while the filtrate was entirely negative even with doses equivalent to 8 cc. of serum (Table 1, b).

C. Effect of Dialyzing Serum

One hundred cc. of the serum was placed in a collodion bag and dialyzed against running tap water for 24 hours. The serum remaining in the bag was tested using the usual graded doses and found to be unchanged in potency.

A continuous dialysis of a sample of the same serum was made at reduced pressure, according to the method described by Hanke and Koessler (43). The membrane used was collodion, and the temperature in the boiling flask never exceeded 38° C. The dialysis was continued for 8 hours, when the dialysate was removed and concentrated in a vacuum at 38° C., to 1/9 of the original volume of serum used. One cc. and 0.5 cc., representing 9 and 4.5 cc. of the serum, respectively, were found to be entirely negative. The residue in the sack still gave a maximum reaction when given in doses of 5 cc.

Zondek and Aschheim (4), and Collip (2) have reported that their active material dialyses readily. It seems evident from this single experiment that the active principle in the blood serum of pregnant mares is either not identical with that obtained from human urine or human placenta or is contained in the blood serum in combination with some larger molecule, such as globulin, which prevents its dialysis through collodion.

D. Effect of Sodium Sulfate on Active Serum

In a previous experiment we found that saturating the serum with sodium sulfate removed the hormone completely. We therefore attempted fractionation of the serum with varying concentrations of sodium sulfate to determine if the principle were carried down with some particular protein fraction. Sodium sulfate seemed preferable to ammonium sulfate for this purpose since nitrogen determinations could be made on the filtrate to indicate the amount of protein removed. However, the limited solubility of this salt at room temperature made it necessary to carry out the work in the 38° room. The results of these fractionations are summarized

in Table II. The first three results were obtained with precipitates from 14, 16, and 18 per cent sodium sulfate, respectively, while the remaining fractions were obtained by increasing the concentration of sodium sulfate

TABLE II

THE REACTION OBTAINED UPON THE OVARIES OF IMMATURE RATS INJECTED WITH VARIOUS FRACTIONS OF BLOOD SERUM TREATED WITH SODIUM SULFATE

Fraction Tested	Reaction Obtained*
Precipitate from 14% sodium sulfate	—
Precipitate from 16% sodium sulfate	+
Precipitate from 18% sodium sulfate	+
Precipitate salting out between 14% and 17% Na_2SO_4	+
Precipitate salting out between 18% and 20% Na_2SO_4	—
Precipitate salting out between 17% and 22% Na_2SO_4	+++
Filtrate containing 22% Na_2SO_4	+ (very slight)
Precipitate salting out between 20% and 27.5% Na_2SO_4	+++
Filtrate containing 27.5% Na_2SO_4	—
Precipitate salting out between 22% and saturated	+

* — Indicates a negative reaction.
\+ Indicates a slight development of the ovaries.
+++ Indicates a maximum ovarian reaction.

in the various filtrates as indicated. For example, after the serum containing 14 per cent sodium sulfate was filtered, the concentration of salt in this filtrate was then increased to 17 per cent and a second precipitate removed. This constituted the fraction salted out between 14 and 17 per cent sodium sulfate. The filtrate was then further saturated to remove the next fraction. In each case, the precipitates were taken up with distilled water and the excess sodium sulfate dialyzed out through a collodion membrane. The activity of each fraction is shown by + and — signs, a slight reaction being indicated by a single + while a reaction comparable with the original serum is indicated by +++. It is apparent that most of the principle is salted out between the limits of 20 and 27 per cent sodium sulfate. Moreover, since the filtrate from the 22 per cent solution was found to be only slightly positive, it is probable that the limits of salting out are even narrower, perhaps between 20 and 25 per cent. This zone includes the pseudoglobulin II of Howe (44). The fraction between the limits of 20 and 27 per cent contains only 11 per cent of the total protein of the serum. It is obvious, therefore, that a large part of the protein may be separated from the hormone in this manner.

Serial sections of the ovaries of the rats receiving the precipitates have revealed two types of ovarian responses. The ovaries of the rats receiving the 0-16, 0-18 or 14-17 per cent precipitates are only slightly enlarged as has been previously noted. In each of these ovaries one usually encounters a single well developed corpus luteum. The remaining portion of the ovary is still infantile in appearance and many primordial follicles may be seen in the outer portion of the ovary. In only a single instance was an ovum found in the tube. The ovaries of the rats receiving the 17-22 or 20-22 per cent precipitates do not contain fully developed corpora. Instead, the ovaries are filled with large follicles, many of which are in primitive stages of luteinization. Very few primordial follicles are

present. These two types of responses are illustrated in figures 1 and 2. The uteri and vaginae of both groups showed typical oestrous develop-

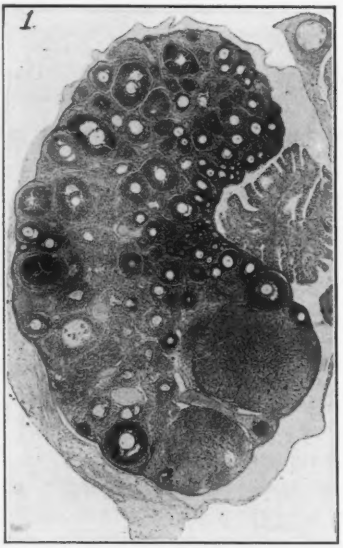

Figure 1. Photomicrograph of a cross-section of an ovary from Rat W1420 receiving the 18 per cent sodium sulfate precipitate. Two corpora lutea are present, but the remaining portion of the ovary is infantile in appearance. x20.

Figure 2. Photomicrograph of a cross-section of an ovary from Rat G1a receiving the 22 per cent sodium sulfate precipitate. The dosage in terms of amounts of original serum was the same as that for Rat W1420. The ovary is filled with large follicles, many of which are in primitive stages of luteinization. x20.

ment. It is possible that these two reactions are merely the result of quantitative differences of a single hormone or it may be that fractional precipitation is accomplishing a partial separation of two hormones.

E. Effect of Heat on Ovary-stimulating Substance

A portion of the material precipitated from the serum by 18 per cent sodium sulfate was made up in water solution and subjected to heating for varying periods and temperatures. Heating for 12 hours at 45° did not destroy the activity of this fraction, but heating to 60° for 30 minutes rendered the solution inactive. With a similar solution made from the more potent precipitate removed by 16-27 per cent Na_2SO_4, heating at 60° for 30 minutes did not seem to cause any change in the activity of the fraction. Both solutions coagulated when heated to 79° C. Bringing untreated blood serum (this sample had been stored for one year at 32-34° C.) to its coagulation point (71° C.) had no detectable effect upon the ovary-stimulating substance.* Further heating of this coagulum at 71° C. for 30 minutes did not diminish its potency. Bringing the temperature of this same sample of serum to that of a boiling water bath and holding it at this temperature for 10 minutes reduced the potency of the serum but did not completely destroy it. Dickens (6) and Zondek and Aschheim (4) found that the active substance in urine of pregnant women is injured by heating to 60° C. Collip's purified material from placenta (2) is not appreciably affected by boiling for 5 minutes in dilute acetic acid solution.

F. Effect of Peptic and Tryptic Digestion

Experiments with pepsin and trypsin digestion did not yield definite results. It was hoped that by means of enzymes, an active fraction might be split off that would dialyze. However, this did not prove to be the case. An active serum was adjusted to pH 3 with hydrochloric acid and then 0.4 per cent dry pepsin added. After digestion at 38° for 12 hours, the reaction of the mixture was again adjusted to pH 7.4 and dialyzed in a collodion bag. Neither the residue nor the dialysate showed any activity when injected. If the digestion was carried on at pH 6 instead of pH 3, some activity remained even after 24 hours at 38° C. However, the active substance did not dialyze but remained in the sack. The results with trypsin were inconclusive. We therefore attempted to establish the resistance of the hormone to enzymes by feeding.

Large doses of active serum were incorporated in the diet of immature rats. This was done by adding a serum, concentrated to one-fourth its original volume. In this way doses of 90 cc. of original serum were consumed by the rats in a period of 3 days. Vaginal and ovarian reactions were completely negative in every case, with doses ranging from 5 to 90 cc. of potent serum. More work needs to be done in order to establish the

*We found that there was a very poor absorption of this coagulum when injected subcutaneously. Upon autopsy we removed this coagulum from the subcutaneous area of one animal and reinjected it into another 21-day-old rat. The reinjected material was still potent, indicating that the absorption of the hormone was very slow. Thus it would appear that a single injection of coagulated serum would be equivalent to several successive injections of the same quantity of untreated serum.

resistance of the ovary-stimulating substance in mare serum to enzyme activity.

SUMMARY AND CONCLUSIONS

Studies were made on the chemical properties of the ovary-stimulating substance occurring in the blood serum of pregnant mares. The serum was collected between the 56th and 132nd day of pregnancy. It was found that the serum could be concentrated at low temperatures in a partial vacuum without an appreciable loss of potency. The active fraction did not pass through a collodion membrane when the serum was ultra-filtered or dialyzed. An active fraction was removed from the serum by precipitating the serum with 14-17 per cent Na_2SO_4. This fraction caused very little increased development of the ovaries of the injected rats. Usually a single corpus luteum was formed in one or both of the ovaries. Only one instance of ovulation was found. The precipitate from 17-22 per cent Na_2SO_4 contained an active fraction which produced reactions similar to the untreated serum when given in equivalent doses. The ovaries were filled with large follicles, many of which were in initial stages of luteinization. It is still not clear whether fractional precipitation accomplishes a partial separation of two factors. It is possible that the results obtained are merely the result of quantitative differences. Heating the serum proteins to the coagulation point did not destroy the potency of the precipitate. Heating the serum to boiling did not completely inactivate the ovary-stimulating substance.

The results obtained by digesting serum with pepsin and trypsin were not consistent. Feeding immature rats doses equivalent to several hundred times the amount necessary to produce a reaction by subcutaneous injection was entirely without effect.

BIBLIOGRAPHY

1. Cole, H. H. and G. H. Hart: The potency of blood serum of mares in progressive stages of pregnancy in effecting the sexual maturity of the immature rat. Am. J. Physiol. **93:** 57. 1930.
2. Collip, J. B.: Further observations on an overy-stimulating hormone of the placenta. Canad. M. A. J. **22:** 761. 1930.
3. Zondek, B.: Hormonale Schwangerschaftsreaktion aus dem Harn bei Mensch und Tier. Klin. Wchnschr. **9:** 2285. 1930.
4. Zondek, B. and S. Aschheim: Das Hormone des Hypophysenvorderlappens. Darstellung, chemische Eigenschaften, biologische Wirkungen. Klin. Wchnschr. **7:** 831. 1928.
5. Zondek, B.: Hypophysenvorderlappen. Arch. f. Gynäk. **144:** 133. 1930.
6. Dickens, F.: The preparation and properties of the gonad-stimulating hormone from the urine of pregnancy. Biochem. J. **24:** 1507. 1930.
7. Reiss, M., A. Schäffner and F. Haurowitz: Über die Inaktivierung des aus Schwangerenharn gewonnenen Hypophysenvorderlappenhormons durch proteolytische Enzyme. Endokrinologie, **8:** 22. 1931.
8. Reichert, F. L., R. I. Pencharz, Miriam E. Simpson, K. Meyer and H. M. Evans: Ineffectiveness of Prolan in hypophysectomized animals. Proc. Soc. Exper. Biol. & Med. **28:** 843. 1931.
9. Evans, H. M., K. Meyer and Miriam E. Simpson: The relation of Prolan to the anterior hypophyseal hormones. Proc. Soc. Exper. Biol. & Med. **28:** 845. 1931.
10. Fevold, H. L., F. L. Hisaw and S. L. Leonard: The gonad-stimulating and the luteinizing hormones of the anterior lobe of the hypophysis. Am. J. Physiol. **97:** 291. 1931.
11. Claus, Pearl E.: Separation of anterior lobe substances and study of their individual effects. Physiol. Zoöl. **4:** 36. 1931.

12. Collip, J. B.: The ovary-stimulating hormone of the placenta. Nature, **125**: 444. 1930.

13. Collip, J. B.: The ovary-stimulating hormone of the placenta. Preliminary paper. Canad. M. A. J. **22**: 215. 1930.

14. Smith, P. E. and C. Dortzbach: The first appearance in the anterior pituitary of the developing pig foetus of detectable amounts of the hormones stimulating ovarian maturity and general body growth. Anat. Rec. **43**: 277. 1929.

15. Smith, P. E. and E. T. Engle: Evidence of a correlation between the amount of gonadal-stimulating hormone present in the pituitary of the guinea pig and the stage of the reproductive cycle. Anat. Rec. **42**: 38. 1929.

16. Evans, H. M. and Miriam E. Simpson: The effect of pregnancy on the anterior hypophysis of the rat and cow as judged by the capacity of implants to produce precocious maturity. Am. J. Physiol. **89**: 379. 1929.

17. Philipp, E.: Hypophysenvorderlappen und Placenta. Zenträlbl. f. Gynäk. **54**: 450. 1930.

18. Evans, H. M. and Miriam E. Simpson: A sex difference in the hormone content of the anterior hypophysis of the rat. Am. J. Physiol. **89**: 375. 1929.

19. Engle, E. T.: The effect of daily transplants of the anterior lobe from gonadectomized rats upon immature test animals. Am. J. Physiol. **88**: 101. 1929.

20. Evans, H. M. and Miriam E. Simpson: A comparison of anterior hypophyseal implants from normal and gonadectomized animals with reference to their capacity to stimulate the immature ovary. Am. J. Physiol. **89**: 371. 1929.

21. Zondek, B.: Über die Hormone des Hypophysenvorderlappens. II Follikelreifungshormon (Prolan A)—Klimakterium.—Kastration. Klin. Wchnschr. **9**: 393. 1930.

22. Zondek, B.: Über die Hormone des Hypophysenvorderlappens. III Follikelreifungshormon (Prolan A) und Tumoren. Klin. Wchnschr. **9**: 679. 1930.

23. Aschheim, S. and B. Zondek: Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenshormons. Klin. Wchnschr. **7**: 1404. 1928.

24. Zondek, B.: Zur Methodik der Schwangerschaftsreaktion aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons. 1 Fällungsschnellreaktion. 2 Entgiftung des Harns. Verbesserung der Schwangerschaftsreaktion. Klin. Wchnschr. **9**: 964. 1930.

25. Baniecki, H.: Schwangerschaftshypophyse und Ovarialhormone. Arch. für Gynäk. **134**: 693. 1928.

26. Charipper, H. A. and H. O. Haterius: The histology of the anterior pituitary of the albino rat in relation to the oestrous cycle. Anat. Rec. **45**: 210. 1930.

27. Nelson, W. O.: A study of the histology of the anterior pituitary of the foetal pig, with reference to growth and maturity. Proc. Soc. Exper. Biol. & Med. **27**: 596. 1930.

28. Evans, H. M. and Miriam E. Simpson: Different effects secured from intraperitoneal as contrasted with subcutaneous administration of the anterior hypophyseal hormones. Anat. Rec. **45**: 215. 1930.

29. Friedman, M. H.: Mechanism of ovulation in the rabbit. II Ovulation produced by the injection of urine from pregnant women. Am. J. Physiol. **90**: 617. 1929.

30. Engle, E. T. and P. E. Smith: The origin of the corpus luteum as indicated by studies upon the luteinization of the cystic follicles. Anat. Rec. **43**: 239. 1929.

31. Engle, E. T.: The relationship between first oestrous, mating, and ovulation in young female mice after anterior-lobe implants. Anat. Rec. **48**: (supplement), 17. 1931.

32. Evans, H. M. and Miriam E. Simpson: A comparison of the ovarian changes produced in immature animals by implants of hypophyseal tissue and hormone from the urine of pregnant women. Am. J. Physiol. **89**: 381. 1929.

33. Smith, P. E. and E. T. Engle: Experimental evidence regarding the rôle of the anterior pituitary in the development and regulation of the genital system. Am. J. Anat. **40**: 159. 1927.

34. Engle, E. T. and Camille Mermod: The action of the gonad-stimulating hormone of the anterior lobe on the course of pregnancy in the rat or mouse. Anat. Rec. **38**: 11. 1928.

35. Kelly, G. L.: The effect of anterior pituitary on conception and pregnancy in the guinea pig. Anat. Rec. **48**: (supplement), 50. 1931.

36. Riddle, O. and Florence Flemion: Studies on the physiology of reproduction in birds. XXVI. The rôle of the anterior pituitary in hastening sexual maturity in ring doves. Am. J. Physiol. **87**: 110. 1928.

37. Burns, R. K., Jr., and Adrian Buyse: The effect of administration of the anterior hypophysis upon the immature gonads of Amblystoma larvae. Anat. Rec. **48**: (supplement), 12. 1931.

38. Zondek, B.: Weitere Untersuchungen zur Darstellung, Biologie, und Klinik des Hypophysenvorderlappenhormons (Prolan). Klin. Wchnschr. **8**: 157. 1929.

39. Mason, K. E. and J. M. Wolfe: The physiological activity of the hypophyses of rats under various experimental conditions. Anat. Rec. **45**: 233. 1930.

40. Meyer, R. K., S. L. Leonard, F. L. Hisaw and S. J. Martin: Effect of oestrin on gonad-stimulating power of the hypophysis. Proc. Soc. Exper. Biol. & Med. **27:** 702. 1930.

41. Fee, A. R. and A. S. Parkes: Studies on ovulation. 1 The relation of the anterior hypophysis to ovulation in the rabbit. J. Physiol. **67:** 383. 1929.

42. Deanesly, Ruth, the late A. R. Fee and A. S. Parkes: Studies on ovulation. II. The effect of hypophysectomy on the formation of the corpus luteum. J. Physiol. **70:** 38. 1930.

43. Hanke, M. T. and K. K. Koessler: A continuous dialysis or extraction apparatus which operates at reduced pressure with a constant volume of liquid. J. Biol. Chem. **66:** 495. 1925.

44. Howe, P. E.: The use of sodium sulfate as the globulin precipitant in the determination of proteins in blood. J. Biol. Chem. 49: **93.** 1921.

HYPERTHYROIDISM AND DIABETES MELLITUS

WITH A REPORT OF NINE CASES*

A. MORRIS GINSBERG, M.D., F.A.C.P.
KANSAS CITY, MO.

An impression one is likely to carry away while reading the clinical journals is, that there is very little, if any, relationship between the two diseases, hyperthyroidism and diabetes mellitus. This opinion completely ignores the experiments which have been carried out since Mering and Minkowski (1), in 1899, extirpated the pancreas for the purpose of seeing whether a certain fat "lipanin" could be absorbed in the absence of a pancreas. Thus was produced experimentally the prototype of diabetes in man. When sugar was administered to these experimental animals, it all appeared in the urine. From this observation these workers concluded that the metabolic fault was that sugar could not be oxidized without the pancreas. However, in 1855, Claude Bernard (2) deduced from his experimental work that diabetes mellitus was the result of an increased sugar production by the liver. Thus the age-old controversy whether the mechanism of diabetes mellitus is due to inability of the organism to oxidize carbohydrates or whether it is due to the "overproduction" of glucose from protein and possibly fat, is still "hanging fire" (3, 4).

When the liver of a depancreatized dog is removed, there is a rapid disappearance of blood sugar (5, 6). This is true of normal animals as well. These observations prove that the blood sugar of both the normal and the diabetic animal is maintained by the liver. It is significant that nearly all the known hyperglycemias are dependent upon the glycogen content of the liver.

If we should believe in the secretory conception of liver function as Cramer (7) would have us believe, then, of course, the glycogen-free liver of the diabetic organism corresponds to the glycogen-free liver of the organism suffering with hyperthyroidism.

Mann and Magath (6) have shown that hepatectomy and administration of insulin to normal animals as found by Banting and his coworkers (8) offer a close similarity, the only difference being that in hepatectomy, glucose administration will relieve the symptoms only temporarily. This is brought out in the following tabular presentation:

Hepatectomy	Insulin to normal animals
Hypoglycemia	Hypoglycemia
Characteristic group of symptoms.	Characteristic group of symptoms.
Glucose effective in relieving symptoms.	Glucose effective in relieving symptoms.
Glucose administration, a temporary relief.	Glucose administration, a permanent relief.

*Read before the Annual Meeting of the American Association for the Study of Goiter, Kansas City, Missouri, April 7, 8, 9, 1931.

It is not likely that experimentally we have ever produced in animals the Graves' syndrome as seen in man (9, 10, 11), but we have been able by excessive thyroid dosage to produce certain results which are also findings in the Graves' syndrome. The results, it is to be remembered, are variable and not constant.

	Experimental Hyperthyroidism	Diabetes Mellitus
Fasting blood sugar	Normal (very important)	Increased
Glycosuria	Absent	Present
Basal metabolism	Increased	Not increased (except in emaciated persons)
Weight	Loss	Loss
Respiratory quotient	Low	Low
Protein metabolism	Increased	Increased
Liver glycogen	Diminished or absent	Diminished or absent

We note above that experimental hyperthyroidism and diabetes mellitus are much alike, differing only as to fasting blood sugar, glycosuria and basal metabolism. In other words, the fundamental difference, in these two conditions, is that in experimental hyperthyroidism more carbohydrate is oxidized than in diabetes mellitus.

Cramer and Krause (12) found that oral administration of fresh thyroid to cats and rats decreased the liver glycogen to a minimum. Kuriyama (13) confirmed this and obtained the same results even with a high carbohydrate diet; he found that when he omitted the thyroid from the diet, the glycogen content reappeared in two to three days. Large doses of adrenalin injections have been responsible for the finding of minimal glycogen deposits in the liver (14, 15). I shall not discuss at any great length the hundreds of other productive experiments, but merely stress the fact that there are definite relationships among the endocrine glands that control metabolism. The thyroid and the suprarenals bear a close relationship. When fresh thyroid is fed to animals, cats and rats, there is produced an increase of size and weight in the suprarenals of both young and adult animals (16). It has been found that injections of B-tetrahydronaphthylamine produces a prolonged adrenalin secretion (17, 18). The results of such an experiment are increased heat production, increased blood sugar, decreased liver glycogen, and increased nitrogen excretion. The latter is a late finding. These metabolic changes are, in fact, qualitatively the same as those produced in experimental hyperthyroidism.

It is well to remember here that overdosage of thyroid in man produces many of the symptoms of sympathetic stimulation as induced by injections of adrenalin. This is the reason that some clinicians believe that symptoms in hyperthyroidism are really caused by overactivity of the adrenals. Palpitation, tachycardia, dilated pupils, prominence of eyeballs, concomitant widening of the palpebral fissure, perspiration and gly-

cosuria are the characteristic symptoms found in both of these gland stimulations.

The two conditions, hyperthyroidism and diabetes, offer similarity, not only experimentally but clinically as well. Joslin (19) emphasizes this similarity when he says that often a patient will come on his diabetic service when he really belongs on Lahey's thyroid service. It is reasonable to understand that such a condition would arise since symptoms in both diseases are so nearly similar. These symptoms are loss of weight, flushed skin, high metabolism, increased pulse rate, weakness, polyuria and thirst.

Sixty-four years have elapsed since this combination was first described. In 1867 Dumontpallier (20) described exophthalmic goiter and diabetes in the same patient. In 1874 Brunton (21) reported a case in the English literature. In 1878 Hartman (22) described two cases from the Tübingen clinic. In 1891 Budde (23) of Denmark reported two cases. In 1899 Manges (24) noted such a combination in a patient and this case was the first to be reported in America. Even though sixty-four years have elapsed relatively few cases have been reported. John (25) collected, from a most thorough search of the literature up to 1927, 137 cases. Joslin and Lahey (26) report 75 cases, Wilder (27) 38 cases and Rabinowitz (28) 24 cases. At the University of Kansas, we have had six cases in 277 cases of hyperthyroidism. The association of hyperthyroidism and diabetes mellitus, as Fitz (29) pointed out ten years ago, is certainly not common.

The fasting blood sugar is clinically of outstanding importance. It is rare to see a fasting blood sugar over 120 mgm. per 100 cc. in an uncomplicated case of hyperthyroidism (30, 31). This finding is a good diagnostic point.

The glucose tolerance test is not characteristic in uncomplicated hyperthyroidism. Tachau (32) was the first to find hyperglycemia in Morbus Basedow; he, though, did not find it a constant symptom. Later many observers (31, 33, 34, 35, 36, 37, 38, 39, 40) reported their findings and it is not surprising to find different reports as to the frequency of hyperglycemia in this highly unstable syndrome. The response to the ingestion of 100 gms. of glucose on a fasting stomach ranges from a normal curve to a typical diabetic curve. When the response is abnormal, the peak is reached after an hour and usually remains elevated after two hours. It is important to remember, in this connection, that there exists no relationship between severity of symptoms and degree of hyperglycemia. In other words, a mild case may show a severe diabetic-like curve, and a severe case of hyperthyroidism may give a normal curve.

Glycosuria may or may not be present in hyperthyroidism; it depends on the so-called renal threshold and the degree of hyperglycemia. There is evidence clinically that the renal threshold is lowered in some cases. Chvostek (41) found a spontaneous and alimentary glycosuria in a high percentage of his Basedow patients. Kocher (42) found it to be frequent.

Wilder and Sansum (43) have shown that, in the hyperthyroid patient, intravenous glucose given, at a uniform rate, provokes a glycosuria more readily.

Joslin (19) aptly advises raising the standard for a diagnosis of diabetes when associated with hyperthyroidism. He says that these cases must present, in addition to the characteristic symptoms of diabetes, a fasting blood sugar of 150 mgm. per 100 cc. and a blood sugar after a meal of 200 mgm. or over per 100 cc. together with glycosuria.

The respiratory quotient following ingestion of glucose has been used as a help in differential diagnosis (35). Whether this test is of any value is problematical, since it has been recently shown experimentally that it is possible to maintain a respiratory quotient in a depancreatized dog far above the "diabetic level" for as long as two weeks (44). A test based on Allen's Paradoxical Law has been recommended (28); in the normal individual there simply is no limit to the assimilation of glucose.

Certainly, the failure of hyperglycemia to rise proportionately to the increased metabolism occasioned by the intensity of thyrotoxicosis leads one to conclude that the toxic action of the thyroid is not a direct phenomenon as far as carbohydrate metabolism is concerned. A patient showing an abnormal curve with or without glycosuria should be carefully watched both before and after operation. Holst (45) goes one step further and says that every diabetic should have a basal metabolism test and every hyperthyroid a sugar analysis.

As far back as 1897 it was noted by Grawitz (46) that feeding thyroid to diabetics aggravated the glycosuria which persisted for some time after thyroid was discontinued. Von Noorden (4) found that feeding thyroid to a mild diabetic increased the glycosuria; in severe diabetes, the difference was too slight to be considered. Bodansky (47) gave subcutaneous injections of thyroxin to sheep and noted an increased blood sugar. Hancher (48) and his co-workers produced a marked and sustained rise in blood sugar when they administered glycerol extract of hashed thyroid gland orally to dogs.

The value of iodine in hyperthyroidism is well established. Labbé (49) deserves the credit for noting that iodine administration in hyperthyroidism helped the associated diabetes by reducing glycosuria. The tachycardia and palpitation were markedly improved. The beneficial effect of iodine on the carbohydrate metabolism is probably a secondary one due to a lowering of the general metabolism.

The following case came to my direct attention and shows the value of iodine medication:

Case 1. H. W., Female, aged 29. The past medical history included measles and tonsillitis in 1926. In 1928 the feet were swollen and a doctor told her she had diabetes. The presenting complaint was loss of weight, polyphagia, polydipsia, polyuria, weakness and nervousness. "Thinks her nervousness was caused by diabetes."

March 14, 1929. The glucose tolerance was fasting, 146 mgm. per 100 cc.; one hour, 363 mgm.; two hours, 444 mgm.; three hours, 400 mgm.; the basal metabolic rate was plus 39 to plus 41; glycosuria four per cent. She was given Lugol's Solution and a diet. She returned twenty months later, November 12, 1930, with no complaints. The fasting blood sugar was 116 mgm. per 100 cc.; the basal metabolic rate was plus five. A second entrance showed a normal fasting sugar.

Furthermore, to emphasize the value of eliminating or depressing thyroid activity upon the course of associated diabetes, attention should be called to certain experiments. Among these are those performed by Friedman and Gottesman (50) and others (51, 52), who found that ligation of the thyroid arteries in depancreatized dogs leads to a disappearance of glycosuria and a decrease of blood sugar in from one to five days and that total thyroidectomy produces the same results. Falta (35) was the first to treat patients suffering with hyperthyroidism and diabetes by x-ray and noted that the glycosuria disappeared.

The following case illustrates what thyroidectomy does to associated diabetes:

Case 2. A. N., Female, aged 47. The past medical history included frequent colds and sore throat; enlargement of the neck for thirty years. The presenting complaint was nervousness, loss of weight and, for the last two months, palpitation. Physical examination revealed a nervous woman with an enlarged, hard, nodular thyroid gland. The heart rate was rapid.

Nov. 10, 1930. The fasting blood sugar was 303 mgm. per 100 cc.; glycosuria, 1.7 per cent; basal metabolic rate, plus thirty-one. Nov. 26, 1930, subtotal thyroidectomy was performed. Nov. 28, 1930, CO_2 combining power was normal. Dec. 12, 1930, CO_2 combining power was normal. Blood sugar, fasting was 143 mgm. per 100 cc. with thirty units of insulin.

Our knowledge of the subject today allows only the inference that thyroidectomy improves the carbohydrate tolerance; it does not cure the diabetes. This is in line with Naunyn's (54) and Von Noorden's (4) views on this subject: that diabetes mellitus is produced only where there is a predisposition to it (Anlage). The deductions Burn and Marks (55) drew from their experiments was that thyroidectomy diminished the readiness of the liver to convert the glycogen into sugar. Though Epstein and Aschener (56) noted that anesthesias lasting one hour or more produced a marked increase of blood sugar, it is well to remember in thyroid surgery, we might encounter a hypoglycemia such as Holman (57) reports.

Doucheneau (58) showed that thyroidectomy makes rabbits more sensitive to insulin. Burn and Marks (55) confirmed this. They felt that the liver liberates glycogen stores to antagonize hypoglycemia produced by excess of insulin. Section of the splanchnics as well as thyroidectomy diminish the compensating action; on the other hand, it is increased by thyroid feeding as long as the glycogen store lasts—but when the reserve is exhausted, no antagonistic action is present. Bodansky (47) found that in thyroidectomized sheep the decrease of blood sugar with insulin was more prolonged and more intense and the recovery to normal values was slower than in normal sheep. He thus concluded that thyroid secretion is essential to normal recovery from insulin hypogly-

cemia. Lawrence (59) treated two cases of exophthalmic goiter with insulin only and noted marked improvement of all symptoms. Thomson (60) treated a case of acute Graves' disease with daily administration of twenty units of insulin and found that the exophthalmos entirely disappeared; the heart rate became regular and the thyroid decreased in size. Lawrence and Buckley (61) found that the action of insulin was antagonized by some bacterial toxins. We have seen that when diabetes is complicated by an infection, the insulin requirement is increased. The same is true of the diabetes which is complicated by hyperthyroidism. It is well to note here that six to twenty-four hours post-operatively, due to a probable overflowing of the system with thyroid secretion, the complicating diabetes will become more severe. Large doses of insulin are necessary for recovery.

The seriousness and the frequency of complicating coma has been brought to our attention by many clinicians. In 1909, Sattler (62) collected 56 reported cases of hyperthyroidism and diabetes, only 37 of which could be followed. Twenty-five of these ended fatally within a short time, and seven died in coma. In view of the high general metabolism and the low glycogen reserve, we expect acidosis to be more easily induced in combined hyperthyroidism and diabetes than in an uncomplicated diabetes. Joslin's (19) statistics show that coma deaths in this dual association are two and one-half times more frequent than in uncomplicated diabetes. This complication is illustrated by the three cases which follow.

Case 3. C. G., Female, aged 20. The past medical history included typhoid and diphtheria in childhood. Two years ago, after the extraction of a third molar, she went into diabetic coma. Six months ago she gave birth to a seven-months' baby and then went into coma again. Two months ago her fasting blood sugar was 396 mgm. per 100 cc. and she was taking sixty units of insulin. She entered the hospital at 2:40 a. m. in insulin shock. Her blood sugar at 3:00 a. m. was 25 mgm. per 100 cc. Three days later her basal metabolism was plus 26. Forty units of insulin was sufficient for a liberal diet. This case illustrates ease of going into acidosis.

Case 4. E. R., Female, aged 18. The past medical history was negative. The presenting complaint was marked nervousness, weakness, polydipsia and loss of weight. These symptoms were present for four months. Physical examination revealed a markedly emaciated girl with all the classical eye findings of exophthalmic goiter together with a diffuse enlargement of the thyroid and a rapid irregular heart action. There was an abscess of the right buttock. The next day she died suddenly. On this day her fasting blood sugar was 333 mgm. per 100 cc. and CO_2 combining power was ten volumes per cent. Autopsy revealed pancreatic changes, exophthalmic goiter, persistent thymus and cellulitis and suppuration of right buttock.

Case 5. E. W., Male, aged 27. The past medical history included measles in childhood. Three years ago he had been in the hospital for several weeks for diabetes. One year ago he came into the hospital with a basal metabolism of 130 and a fasting blood sugar of 250. In 1921, ligation of both superior thyroid arteries was performed and the patient left the hospital feeling fine. The presenting complaint was chills. Physical examination revealed nothing to account for the chills. He had acetone and diacetic acid in the urine. He died three days after admission in acidosis (1922).

These patients have many varied complaints. The following cases illustrate this fact.

Case 6. T. N. C., Female, aged 50. The past medical history included gall bladder operation, appendectomy, right oophorectomy and salpingectomy in 1917. She had had her teeth out a little later. In 1919, a doctor told her she had goiter and diabetes. The presenting complaint was heart trouble and pain in the stomach. Physical examination showed a very dyspneic woman with edema of the legs and moderate ascites. The liver was down to the pelvis. The blood pressure was 185/110. The heart sounds were poor and distant. The fasting blood sugar was 238. The basal metabolism was plus 74. She remained in the hospital for 25 days and left decidedly improved.

Case 7. M. C,, Female, aged 43. The past medical history included scarlet fever. The presenting complaint was loss of weight. She had had diabetes for the last year but lately had been restless and had palpitation. She was very nervous. The physical examination showed a woman who had lost weight. There was marked exophthalmos, and a soft, nodular thyroid. The heart rate was rapid. Fasting blood sugar was 209 mgm. per 100 cc. with 1.6 per cent of sugar in the urine. Subtotal thyroidectomy was performed and the pathology report showed definite exophthalmic goiter with almost complete reversion. The next day after the operation the patient showed acetone and diacetic acid. She left the hospital feeling fine and with a fasting blood sugar of 121 mgm.

Case 8. M. B., Female, aged 51. The past medical history showed that the patient had always been obese. The presenting complaint was nervousness, and began one year ago with excessive appetite and thirty pounds loss of weight. She had dyspnea, which improved since taking Lugol's Solution for one month. The basal metabolism upon entrance was plus 13.7. The fasting blood sugar was 172. There was seven-tenths per cent sugar in the urine. Subtotal thyroidectomy was made. The pathological examination showed typical degenerated adematous tissue.

Case 9. L. F., Female, aged 64. The past medical history included removal of a fibroid seven years before. The presenting complaint was numbness in both extremities, pricking of the skin and swelling of the feet at night. Physical examination revealed a large nodular thyroid (thirty years' duration), infected tonsils and incisional hernia. The fasting blood sugar was 210 mgm. per 100 cc. The basal metabolic rate was plus 50. The patient refused operation and improved on a diet and Lugol's Solution.

SUMMARY

1. The mechanism of diabetes mellitus is still an unsettled question.

2. It has been noted experimentally that the liver regulates blood sugar values.

3. Experimental hyperthyroidism and diabetes mellitus are much alike, differing only as to fasting blood sugar, glycosuria and basal metabolism.

4. A review of the literature reveals that there is:

(a) A close relationship between the thyroid gland, the suprarenals, and the glycogen content of the liver;

(b) That oral administration of thyroid substance decreases liver glycogen and increases the size and weight of the suprarenal glands;

(c) That overactivity of the adrenals produce symptoms which are similar to those found in overactivity of the thyroid gland.

5. A review of the literature on the association of hyperthyroidism and diabetes mellitus reveals that comparatively few cases have been reported.

6. The symptoms of clinical hyperthyroidism and diabetes mellitus are so similar that it is not unusual for these two diseases to be mistaken for each other.

7. A diagnosis of hyperthyroidism associated with diabetes mellitus should be made when there is present, beside the characteristic symptoms of diabetes, a fasting blood sugar of 150 mgm. per 100 cc. and after a meal a blood sugar of 200 mgm.

8. Nine illustrative cases are cited.

Note.—Cases one to six, inclusive, are from the medical service of Dr. Ralph Major, Bell Memorial Hospital, University of Kansas. I am indebted to Dr. Kerwin Kinard, Kansas City, Missouri, for cases seven and eight.

BIBLIOGRAPHY

1. Mering, J. von and O. Minkowski: Diabetes Mellitus nach Pancreasexstirpation. Arch. Exp. Path. und Path. **26:** 371. 1889.
2. Bernard, C.: Leçons de physiologie expérimentale. T. B. Bailliere. 1855. P. 89. Paris.
3. Geelmuyden, H. C.: Die Neubildung von Kohlenhydrat im Tierkörper. Ergeb. d. Phys. **22:** 51. 1923.
4. Noorden, C. von and S. Isaac: Die Zuckerkrankheit und ihre Behandlung. Julius Springer. 1927. Berlin.
5. Markowitz, J.: Glyconeogenesis. Am. J. Physiol. **73:** 22. 1925.
6. Mann, F. C. and T. B. Magath: Studies on the physiology of the liver. Am. J. Physiol. **65:** 403. 1923.
7. Cramer, W.: Fever, Heat Regulation, Climate and the Thyroid-Adrenal Apparatus. Longmans, Green and Co., London, 1928.
8. Banting, F. G., C. H. Best, J. B. Collip, J. J. R. Macleod and E. C. Noble: The effect of pancreatic extract (Insulin) on normal rabbits. Am. J. Physiol. **62:** 162. 1922.
9. Biedl, A.: Innere Sekretion. Urban & Schwarzenberg, Berlin and Wien., 1910, p. 89.
10. Carlson, A. J., J. R. Rooks and J. F. McKie: Attempts to produce experimental hyperthyroidism in mammals and birds. Am. J. Physiol. **30:** 129. 1912.
11. French, H. E.: The comparative toxicity of different animal tissues to animals susceptible to thyroid feeding. Am. J. Physiol. **30:** 56. 1912.
12. Cramer, W. and R. A. Krause: Carbohydrate metabolism in its relation to the thyroid gland. The effect of thyroid feeding on the glycogen content of the liver and on the nitrogen distribution in the urine. Proc. Roy. Soc., London, **86:** 550. 1912.
13. Kuriyama, S.: The influence of thyroid upon carbohydrate metabolism. Am. J. Physiol. **43:** 481. 1917.
14. Paton, D. N.: On the nature of adrenalin glycosuria. J. Physiol. **29:** 286. 1903.
15. Wolownik, W.: Experimentelle Untersuchungen über das Adrenalin. Virchow's Arch. f. path. Anat. **180:** 225. 1905.
16. Herring, P. T.: The effect of thyroid feeding on the weight of the suprarenals and on their adrenalin content. Quart. J. Exper. Physiol. **11:** 47. 1917.
17. Cramer, W.: On the thyroid-adrenal apparatus and its function in the heat regulation of the body. Proc. of Physiol. Soc., J. Physiol. **38:** 50. 1916.
18. Elliot, T. R.: The control of the suprarenal glands by the splanchnic nerves. J. Physiol. **44:** 374. 1912.
19. Joslin, E. P.: The Treatment of Diabetes Mellitus. Lea and Febiger, Philadelphia, 1928. p. 878.
20. Dumontpallier: Goitre exophthalmique et glycosurie chéz la même malade. Compt. rend. Soc. de Biol. **4:** 116. 1867.
21. Brunton, L.: Cases of exophthalmic goiter. St. Barth. Hosp. Rep. **10:** 255. 1874.
22. Hartman, C.: Ueber Zwei mit Basedow'scher Krankheit complikirte Falle von Diabetes Mellitus. Inaug. Diss., 1878, p. 24.
23. Budde, V.: See Fitz. Review in Neurol. Centralbl. **10:** 112. 1891.
24. Manges, M.: A case of exophthalmic goiter with diabetes mellitus and pigmentation. Mt. Sinai Hosp. Rep. **2:** 59. 1899.
25. John, H. J.: Carbohydrate metabolism. This Journal, **11:** 497. 1927.
26. Joslin, E. P. and F. Lahey: Diabetes and hyperthyroidism. Am. J. M. Sc. **176:** 1. 1928.
27. Wilder, R. M.: Hyperthyroidism, myxedema and diabetes. Tr. A. Am. Physicians, **41:** 113. 1926.
28. Rabinowitz, I. M.: The glycosuria of hyperthyroidism and its clinical significance. Ann. Int. Med. **4:** 881. 1931.
29. Fitz, R.: The relation of hyperthyroidism to diabetes mellitus. Arch. Int. Med. **27:** 305. 1921.
30. John, H. J.: Differential diagnosis of diabetes by means of glucose tolerance. J. A. M. A. **79:** 1234. 1922.
31. Denis, W., J. C. Aub and A. S. Minot: Blood sugar in hyperthyroidism. Arch. Int. Med. **20:** 964. 1917.
32. Tachau, H.: Über alimentäre Hyperglykämie. Deut. Arch. f. Klin. Med. **104:** 437. 1911.

33. Morris, M. F.: Values of the alimentary test in the diagnosis of mild hyperthyroidism. J. A. M. A. **76:** 1566. 1921.
34. Geyelin, H. R.: The carbohydrate metabolism in hyperthyroidism as determined by examination of blood and urine. Arch. Int. Med. **16:** 975. 1916.
35. Marsh, P. R.: Glycosuria in thyroid disease. Ann. Clin. Med. **16:** 975. 1916.
36. Rohdenburg, G. L., A. Bernhard and O. Kerhbiel: A study of sugar mobilization based upon 228 human subjects. Am. J. M. Sc. **59:** 577. 1920.
37. Sanger, B. J. and E. G. Hun: The glucose mobilization rate in hyperthyroidism. Arch. Int. Med. **30:** 397. 1922.
38. Major, R. H.: Studies on sugar tolerance. Johns Hopkins Hosp. Bull. **34:** 21. 1923.
39. Flesch, M.: Ueber den Blutzucker Gehalt bei Morbus Basedowii und uber thyreogene Hyperglykamie. Beitr. z. klin. Chir. **82:** 236. 1912.
40. Schulze, F.: Ueber die alimentare Glykosurie und adrenalen Glykosurie bei Morbus Basedowii und ihre operative Beeinflussung. Beitr. z. klin. Chir. **82:** 207. 1912.
41. Chvostek, F.: Ueber alimentare Glykosurie bei Basedawii. Wien. klin. Wchnschr. **5:** 267. 1892.
42. Kocher, A.: Ueber Morbus Basedowii. Mitt. a. d. Grenzgeb. d. Med. u. Chir. **9:** 1. 1902.
43. Wilder, R. M. and W. D. Sansum: Glucose tolerance in health and disease. Arch. Int. Med. **19:** 311. 1917.
44. Soskin, S.: The utilization of carbohydrate by totally depancreatized dogs receiving no insulin. J. Nutrition, **3:** 99. 1930.
45. Holst, J.: Glycosuria and diabetes in exophthalmic goiter. Acta Med. Scandinav. **55:** 302. 1921. Abst., J. A. M. A. **9:** 744. 1921.
46. Grawitz, E.: Morbus Basedowii compliziert mit Diabetes Mellitus nebst Bemerkungen uber Iodthyrinwirkung. Fortschr. d. Med. **15:** 489. 1897.
47. Bodansky, A.: Antagonistic effects of insulin and thyroxin. Proc. Soc. Exper. Biol. & Med. **20:** 538. 1923.
48. Hancher, K. G., M. Hupper, N. F. Blau and J. Rogers: The changes in the blood sugar which follow experimental thyroid feeding. Am. J. Physiol. **75:** 1. 1925.
49. Labbé, M.: Diabete et goitre exophthalmique. Ann. d. med. **7:** 95. 1920.
50. Friedman, G. A. and J. Gottesman: Studies on the relation of the thyroid to pancreatic diabetes in dogs. J. A. M. A. **79:** 1929. 1922.
51. Lorand, A.: Les rapport du pancreas (ilots de Langerhans) avec la thyroide. Compt. rend. Soc. de biol. **56:** 488. 1904.
52. McCallum, W. G.: On the relation of the islands of Langerhans to glycosuria. Johns Hopkins Hosp. Bull. **20:** 264. 1909.
53. Falta, W.: Ueber Glykosurie und Fettstuhle bei Morbus Basedowii zugleichen Beitrag zur Röntgen therapie dieser. Krankheit. Zeit Klin. Med. **71:** 1. 1910.
54. Naunyn, B.: Der Diabetes Mellitus. Vienna, 1906. Alfred Hölder. p. 99.
55. Burn, J. H. and H. P. Marks: The relation of the thyroid gland to the action of insulin. J. Physiol. **60:** 131. 1925.
56. Epstein, A. A. and P. W. Aschner: The effect of surgical procedures on the blood sugar content. J. Biol. Chem. **25:** 151. 1916.
57. Holman, E.: Hypoglycemia in exophthalmic goiter. Johns Hopkins Hosp. Bull. **69:** 34. 1923.
58. Doucheneau. See Lawrence, Brit. M. J. **2:** 753. 1924. Compt. rend. Soc. de Biol. **90:** 248. 1924.
59. Lawrence, R. D.: Four cases of exophthalmic goiter treated with insulin. Brit. M. J. **2:** 753. 1924.
60. Thomson, A. P.: Treatment of exophthalmic goiter with insulin. Brit. M. J. **2:** 876. 1924.
61. Lawrence, R. D. and O. B. Buckley: The inhibition of insulin action by toxemias and its explanation. I. The effect of diphtheria toxin on blood sugar and insulin action in rabbits. Brit. J. Exper. Path. **8:** 59. 1927.
62. Sattler: Die Basedow'sche Krankheit, 1909. Engelmann, Leipzig. P. 384.

AN UNUSUAL EFFECT OF A CARBOHYDRATE-RICH, FAT-POOR DIABETIC DIET. REPORT OF A CASE.

P. A. GRAY, M.D., AND W. D. SANSUM, M.D.
SANTA BARBARA, CALIFORNIA

Ever since the days of von Noorden's famous oatmeal cure, the tendency in diabetic diets has been toward greater liberty with carbohydrate-containing food. The beneficial effect of the oatmeal cure and that of its many modifications was variously ascribed to the low protein, the mineral, and the carbohydrate content. After its initial success, interest lagged in rich carbohydrate days until after the discovery of insulin.

Sansum (2) in California and Adlersberg and Porges (1) in Vienna independently revived interest in the possibility of allowing diabetic patients increased amounts of carbohydrate-containing foods. When the carbohydrates were increased, the total calories were maintained constant by a corresponding reduction in the fats. Whether the beneficial clinical results which have been obtained by using these diets are due to the increase in the carbohydrates or to the decrease in the fats is still debatable.

The following case records a rather unusual experience obtained in one instance in which a diet abnormally rich in carbohydrate and correspondingly poor in fat was used:

C. S., aged 45, had been a diabetic for four years. He had had treatment for three years. A cousin had diabetes. There was evidence of old calcified pulmonary tuberculosis. He had had typhoid at 7. Previous surgery had been appendectomy and cholecystectomy. Since beginning diabetic treatment this man's care had been excellent and his cooperation perfect. The following table gives the data of the experiment:

	Date	C	P	F	G	Cal.	Insulin Units	Urine Sugar	Blood Sugar	Weight
								gm.	mgm. %	kgm.
I.	6/ 3/29	217	93	107	282	2203	85	0	246	62.7
	6/12/29	296	91	74	356	2214	72	++	156	62.5
	6/24/29	296	91	74	356	2214	64	0		61.8
II.	6/25/29	431	61	26	469	2202	64	60.9	224	
	6/26/29	431	61	26	469	2202	64	0		
	6/27/29	431	61	26	469	2202	64	1.3		62.3
III.	6/28/29	296	91	74	356	2214	60	2.7	230	
	7/10/29	296	91	74	356	2214	56	0		61.6
IV.	7/11/29	329	142	56	417	2393	56	0	244	62.0
	7/24/29	327	86	82	385	2390	46	11.5		61.8
V.	7/26/29	296	91	74	356	2214	46	0		
	8/ 5/29	296	91	74	356	2214	37	0		61.3
	8/19/29	204	76	97	258	1993	46	0		60.4
	8/26/29	204	76	97	258	1993	43	0	152	

Prior to 1929 he had, under careful diabetic treatment, reached the level of metabolism shown by being able to utilize C 217, P 93, F 107,

G 282, with 85 units of insulin. For some time before beginning the experiment his tolerance had apparently been constant. During the first stage of the experiment the principal change made in his diet was a reduction of 13 gm. F and an increase of 79 gm. C, thereby increasing the "G" value to 356 gm. After three weeks on this diet, his insulin requirement had been lowered to 64 units daily.

On the 25th of June, 1929, with the full knowledge and cooperation of the patient, a radical change was made in his diet. Forty-eight grams F were withdrawn and replaced by 135 gm. C. An attempt was made to keep the substitution exactly equicaloric, but this could not quite be accomplished using food pleasing to the subject. The insulin dosage remained constant. During the first twenty-four hour period, 60.9 gm. of urine sugar were excreted, leaving 408.1 gm. of available glucose for supposed utilization. This represents an excess of 52.1 gm. over the best record of the first or preliminary period. On June 26th the same diet was continued, and during this twenty-four hour period no sugar was excreted in the urine. In the afternoon of June 27th, on the same diet and insulin dosage, the subject experienced symptoms of insulin shock. The twenty-four hour urine specimen contained 1.3 gm. sugar. The fasting blood sugar on June 28th was 230 mgm., as compared to 224 mgm. on June 25th at the beginning of the experiment.

We thought by this observation to have obtained presumptive evidence that on the first day of this abnormally low fat and high carbohydrate diet, 52.1 gm. of available glucose was utilized above that of the preliminary period, and that on the second day 115 gm. extra was utilized. That this additional amount of energy could have been stored as body fat seemed improbable because the patient's body weight only increased 0.5 kilogram. The natural assumption seems to be that some feature of this peculiar diet stimulated the production of an increased amount of endogenous insulin.

If this assumption was true, was this stimulation transitory or relatively lasting? During the third stage of the experiment this patient was placed again on the same diet which he had had during the preliminary period and an attempt was made to lower his insulin requirement. In about two weeks his urine was still sugar-free with 56 units of insulin, although the blood sugar had risen slightly to 244 mgm.

Then an attempt was made to replace the fat with protein instead of carbohydrate, as in the second period. As can be seen from the chart, some effect could be obtained, but by no means as marked as in the second period. Although one is not justified in drawing sweeping conclusions from such a crude experiment, it seems that the combination of low fat, high carbohydrate is more readily utilizable than low fat, high protein. Some further features of this patient's progress are illustrated in the final period.

COMMENT

The remarkable feature of this case is that large amounts of readily absorbable carbohydrate were fed to the patient and were apparently utilized without the necessity of giving additional amounts of insulin. During the three days of the second period he received cake, pie, marmalade, and cane sugar. Several teaspoonfuls of the latter were allowed per meal. The remarkable feature was not that sugar was found in the urine the next morning, but that no more was found. On the next two days the urine was practically sugar-free.

The mechanism underlying this experience is not clear, but may be in line with Adlersberg and Porges' conception of insulin secretion as the response of a complex reflex following stimulation of the buccal mucosa from contact with carbohydrate foods. The additional carbohydrate may have stimulated the secretion of additional insulin. Again there may be some beneficial influence upon the liver by loading it with glycogen. It has been suggested before (von Noorden and Adlersberg and Porges) that the relative proportion of liver glycogen to liver fat may be a factor regulating the secretion of pancreatic insulin. This case was thought to be of enough general interest to warrant publication. We hope that it will prove stimulating in reopening some other questions concerned with carbohydrate metabolism.

SUMMARY

An experiment is recorded in which an abnormally low fat, high carbohydrate diet was tried for three days on a well controlled diabetic male. Some evidence suggestive of increased carbohydrate utilization was obtained.

BIBLIOGRAPHY

1. Adlersberg and Porges: Klin. Wchnschr. **5**: 1451. 1926. Ibid. **6**: 2371. 1927. Ibid. **7**: 1503. 1928.
2. Sansum, et al.: Calif. and West. Med. **22**: 321. 1924.
3. Von Noorden and S. Isaac: Zuckerkrankheit. Julius Springer, 1927.

Abstract Department

Antagonism between epinephrine and ergotamine, and the respiratory quotient (Antagonismo fra adrenalina e ergotamina e ricombio respiratorio). Capo, R., Riforma med. **46:** 1347. 1930. Abst., J. A. M. A. **95:** 1703.

Capo experimented to discover whether ergotamine would counteract the increase of energy exchange caused almost constantly by epinephrine, whether administered fasting or after the ingestion of food (dynamic-specific action). From his researches, he concluded that ergotamine did not modify the greater consumption of oxygen induced by epinephrine but that it did cause, when administered fasting, a notable lowering of the elimination of carbon dioxide and a reduction of the respiratory quotient. His study of the gas exchange demonstrated the antagonistic action that these two substances exert on carbohydrate exchange. Epinephrine caused a mobilization of hepatic glycogen and thus increased almost constantly the elimination of carbon dioxide and raised the respiratory quotient. Ergotamine, on the other hand, inhibited the hyperglycemia that was induced by the epinephrine without modifying the increased intra-organic combustion caused by epinephrine. In other words, under the action of ergotamine, epinephrine, though glycogenolysis is checked, stimulates the cells to a greater combustion, and these cells, not having sufficient carbohydrates at their disposal, burn other reserve substances, namely, the fats, thereby lowering the respiratory quotient.

Does adrenalin have a direct action on the base of the midbrain (Ubt das Adrenalin eine direkte Wirkung auf die Basis des Zwischenhirns aus)? Kahn, R. H. and E. Rindt, Endokrinologie, **8:** 1. 1931.

In 2 cats and 2 dogs the direct application of adrenalin to the surface of the mid-brain gave no significant effect on blood pressure, though direct faradic stimulation called forth a prompt rise of the blood pressure. The conclusion is drawn that adrenalin has no direct effect on the sympathetic centers.

—R. G. H.

Adenoma of the suprarenal medulla with paroxysmal hypertension (L'adenoma medullaire surrenal avec hypertension paroxystique). Labbe, M. P., L. Violle and E. Azerad, Presse méd. **38:** 553. 1930.

The publication of a case of hypertension with tumor of the suprarenal was made by one of the authors, Labbe, with Tinel and Doumer in 1922. The case is quoted again. It was characterized by attacks of vomiting with symptoms of general vasoconstriction and followed by a state of fatigue. The only objective symptom of the attacks was high blood pressure, somewhat irregular in different attacks, rising suddenly from 15/20 to 26/80. The patient died from sudden edema of the lungs and a tumor of the left suprarenal was found. The histological examination revealed a paraganglioma or a medullary adenoma. The article distinguishes between hypertension in paroxysms and permanent paroxysm. Permanent hypertension is usually associated with neoplasm of the suprarenal cortex. The paroxysmal type has symptoms due to the medulla of the suprarenal. The history of a new case is also given. A man 29 years of age had attacks of paroxysmal hypertension with malaise, tachycardia, profuse sweating. The blood pressure rose from 16/10 to 25/30. The attacks started with a feeling of anxiety, pallor, eyes looked haggard, pupils dilated, violent palpitation followed with tachycardia and high blood pressure. The duration of his attacks averaged one hour and was ended by profuse perspiration. They repeated themselves very frequently, sometimes several times a day. After these had existd for four or five years, he had a right-sided hemiplegia in the course of his attacks. Finally he had a permanent albuminuria, acetone and cholesterinemia and died in a very acute attack. The autopsy showed lesions of chronic nephritis (histologically). The left suprarenal gland was normal and weighed 7 grams. The right suprarenal gland weighed 120 grams and was enlarged to about the size of a small orange. The tumor consisted of a structure characteristic of cells of the suprarenal medulla and so named paraganglioma. The article mentions also that constant hypertension is not necessarily due to nephritis alone; in some cases it has been observed in suprarenal tumors of cortical origin. As to the treat-

ment, Sezary and Lomon tried radiation of the suprarenals in Vaquez's case but the improvement was only temporary and did not prevent the fatal termination. He mentions the surgical cure of such a case by Mayo and gives finally a good bibliography of the suprarenal tumors with hypertension. Cures by removal of the tumors by American surgeons such as Shipley and Porter do not seem to be known to the authors.—R. C. Moehlig.

Addison's disease without hypotension (Maladie d'Addison sans hypotension). Legrand, R. and Legillon, Rev. franç. d'endocrinol, **8**: 139. 1930.

A case in which the symptomology was typically of Addison's disease except that hypotension was absent is reported. Postmortem examination showed that medullary substance was practically absent.—B. C.

The effect of adrenaline on the auricle of Elasmobranch fishes. Lutz, B. R., Am. J. Physiol. **94**: 135. 1930. Abst., Physiol. Absts. **15**: 541.

One in 50,000 to 1 in 25,000 adrenaline chloride causes slowing or complete inhibition of the isolated sinus-auricle preparation. It may decrease the amplitude, but both amplitude and rate recover, giving an increase in amplitude over the original basal value.

The influence of adrenal cortex on the development of the female sex organs (Der Einfluss der Hyperinterrenalisierung auf die Entwicklung der weiblichen Geschlechtsorgane). Müller, C., Endokrinologie, **8**: 5. 1931.

The author was interested in the masculinizing influence of the adrenal cortex. Fresh cortex was ground up in a mortar, filtered, heated, aerated to destroy the contained adrenin and injected in young female rats. The series comprised 6 controls, 5 normal injected animals, 10 thymectomized and 10 thymectomized control animals. The results were a rather marked inhibition of sexual development, shown in both the external and internal genitalia. There was an overdevelopment of the ova and a failure of corpus luteum development. The pertinent literature is reviewed.—R. G. H.

Observations on the menopause. III. Sensitiveness of women at the menopause to epinephrine. Myers, W. K. and J. T. King, Jr., Bull. Johns Hopkins Hosp. **47**: 22. 1930.

The response under basal conditions of twenty-four women at the menopause to 10 minims of a 1-1000 solution of epinephrine was studied. In twelve patients who were in the beginning or in the midst of the menopause the response was interpreted as positive. There was an immediate rise in the systolic blood pressure and pulse rate, and subjective disturbances were noted. One patient experienced a "flush" at the height of the reaction. Nine patients gave negative responses. There was no rise or fall in the systolic blood pressure. Eight of these patients were having few symptoms of the menopause at the time. Three patients showed only a slight rise in the systolic blood pressure. Amelioration of the symptoms of the menopause was noted in two of these. No one of ten healthy young women gave a response which could be interpreted as positive. A hypersensitivity of the sympathetic nervous system may exist in a considerable proportion of women who suffer from symptoms of the menopause. Although the type of the response in women resembles that observed in hyperthyroid individuals, there is no evidence in this group that hyperthyroidism played any rôle. The distressing symptoms of the menopause may be the consequence of an increased irritability of the sympathetic nervous system.—W. K. Myers.

Effect of beta-tetrahydronaphthylamin on adrenin secretion (Beta-Tetrahydronaphthylamins auf die Epinephrinabgabe der Nebenniere beim Hunde). Sato, H. and T. Sugawara, Tohoku J. Exper. Med. **16**: 580. 1930.

Beta-tetrahydronaphthylamin was administered intravenously to dogs (ten subjects) in doses of 0.05 to 20 mgm. in various cases. Both anaesthetized and unanaesthetized (deafferented) subjects were used. The adrenin was determined by the caval pocket—intestine assay method. It was found that this drug had only a weak stimulating effect whether anaesthetic was used or not.—R. G. H.

On the site of evanescence of adrenaline in the organism. Sato, H., Tohoku J. Exper. Med. **16**: 597. 1930.

Experiments were made on dogs both with and without anesthesia. The adrenin content of the blood was determined by the intestinal segment and the denervated iris methods. It was found that when adrenaline hydrochloride is given intravenously in a dose of 0.3 mgm. per kilo of body weight, it disappears from the general blood circulation of dogs 5-13 minutes after injecting. The time of disappearance of adrenaline from the general circulation nearly coincides in the averages with the return of the blood pressure to its original level, though in individual cases the coincidence is not always so exact. Adrenaline was much more rapidly destroyed in the arterial blood, shut up instantaneously in an artery in situ, in comparison with the blood taken out and rendered non-coagulable, either mechanically or chemically. The velocity of disappearance of adrenaline in the venous blood, similarly treated, was less than that in the arterial. The velocity of diminution of adrenaline in the living animal occurred generally by geometrical progression, while the rate of the recovery of the mean blood pressure was directly elapsed interval or somewhat slower.—R. G. H.

The effect of bilateral suprarenalectomy on the oestrus cycle in the albino rat. Schiffer, A. L., Proc. Ohio Acad. Sc. **8**: 414. 1930.

A series of twenty adrenalectomies were performed to determine the relationship between the adrenal gland and the oestrus cycle in albino rats. Daily vaginal smears were started November 3rd, 1929, and taken for three weeks previous to removal of both adrenal glands. These smears were continued through the operative period and up to February 16th, 1930. There were five to seven pre-operative oestrus cycles and ten to thirteen post-operative oestrus cycles. The difference found after averaging the pre-operative cycles and post-operative cycles was not sufficient to warrant any relationship between the adrenal gland and the ovaries as to the oestrus cycle.
—Author's Abst.

The effect of painful stimuli on the secretion of the suprarenals and the blood sugar (Der Einfluss des Schmerzreizes auf die Nebennierensecretion und den Blutzucker). Schtscherbakow, S. A., W. S. Simnitzky, A. A. Wischnewsky and W. R. Dimitrijew, Arch. f. d. ges. Physiol. **224**: 670. 1930. Abst., Physiol. Absts. **15**: 600.

Faradic stimulation of the sciatic nerve causes a rise in the blood sugar. After removal of the suprarenals (clamping of the splanchnic veins or section of the splanchnic nerves), a similar stimulation causes a fall in the blood sugar. Blood removed from the suprarenal vein at the moment of stimulation causes a rise in blood sugar when injected intravenously into another animal. Painful stimuli bring about the mobilization of sugar from the carbohydrate depots through a reflex by way of the splanchnic nerves and suprarenals, and assimilation of the blood sugar in the cells and tissues by way of the vagi and the pancreas.

The influence of extracts of suprarenal cortex on the growth of carcinoma, sarcoma, and melanoma in animals. Sugiura, K., Am. J. Cancer, **15**: 129. 1931.

The toxic action of extracts of suprarenal cortex (sheep and cattle) on the Flexner-Jobling rat carcinoma, the Sugiura rat sarcoma, the Bashford mouse carcinoma No. 63, a transplantable mouse menanomo, and the Rous chicken sarcoma has been investigated. Single or repeated subcutaneous or intramuscular injections of an alcoholic, ether, aqueous, or glycerine extract of the cortical tissues has no apparent influence upon the growth of transplanted tumors. Injection of choline solution or feeding with sodium nitrite, chemicals known to cause a prompt fall of blood pressure, failed to show any inhibiting effect upon the tumor growth. Extracts from the adenomatous growths of sheep suprarenal glands, which are almost completely free from medullary tissue, produced no effect upon the growth of neoplasms. Fresh sheep suprarenal cortex or its extract failed to destroy cancer cells in vitro. The repeated subcutaneous injection of extracts of the suprarenal glands of sheep, of immune and normal young rats, and of suckling rats, does not affect the growth of rat and mouse carcinomas.—K. Sugiura.

The influence of suprarenalin (epinephrin) on the growth of carcinoma and sarcoma in animals. Sugiura, K. and S. R. Benedict, J. Cancer Research, **14**: 487. 1930.

The toxic action of suprarenalin on the Flexner-Jobling rat carcinoma and the Rous chicken sarcoma has been investigated in three different ways, namely, (a) injection directly into and around the tumor, (b) injection subcutaneously at a point away from the tumor and (c) in vitro. The development of small tumors in animals is completely inhibited by repeated intratumoral injections of suprarenalin, while large tumors are seldom beneficially affected by repeated injections. The repeated subcutaneous injection of suprarenalin at a remote point does not affect the growth of rat carcinoma and chicken sarcoma. In vitro experiments indicate that the proliferating capacity of the Flexner-Jobling rat carcinoma was partially destroyed by suprarenalin, but the Rous chicken sarcoma was unaffected as respects its growth after implantation. Hence, it appears probable that the destructive action which suprarenalin exerts upon the tumor is due to its marked vaso-constrictive power.—K. Sugiura.

The action of adrenalin and calcium upon the isolated heart and the blood vessels and their dependence on the change of acid-alkaline equilibrium of the medium (Die Adrenalin und Calziumwirkung auf das isolierte Herz und die Gefasse in Abhangigkeit von der Veranderung des Sauerbasengleichgewichts des Mediums). Treguboff, A. A., Russian J. Endocrinology, **1**: 44. 1930.

On the basis of numerous experiments carried out, according to Beresin's technique, upon the isolated vessels of rabbits' ears and frogs' hearts, the following results have been determined. The acid products of metabolism, which are formed by the action of the calcium and the cells, restrict the systolic actions of the calcium and stop the heart in the diastole. A definite alkalinity of the medium is necessary for the manifestation of the calcium action. An excess causes no noticeable effect, while a decrease in alkalinity causes the gradual extinction of the heart systole. Increased alkalinity causes increased vaso-constrictive action of adrenaline. The addition of alkali aids the maximal action of calcium. Calcium increases the action of adrenalin. Calcium, alkali, and adrenalin effect the same results.—J. Gagnon.

Vagal function in adrenal insufficiency (La funzione vagale nelle insufficienza surrenale). Viale, G., Arch. di fisiol. **28**: 9. 1930. Abst., Physiol. Absts. **15**: 577.

In adrenalectomized dogs, section of the vagi causes slowing of the heart and fall in blood pressure. From this and other experiments it is concluded that the tachycardia which follows vagotomy in normal dogs is due to adrenalinaemia, and not to removal of direct, vagal, tonic influences to the heart.

The part played by the suprarenal capsules in the hyperglycemia produced by decamethyline diguanidine (Rôle des capsules surrénales dans l'hyperglycémie produite par la décaméthylène diguanidine). Zunz, E. and J. La Barre, Compt. rend. Soc. de biol. **103**: 929. 1930. Abst., Rev. belge. sc. méd. **2**: 660.

The hyperglycemia preceding the hypoglycemia caused by the injection of decamethylene diguanidine into the dog is not produced if the animal has been adrenalectomized. The discharge of adrenaline could not be demonstrated by the anastomosis of the suprarenal and jugular vessels according to the technique of Tournade and Chabroe. The experimental animal does not show the characteristic changes of the carotid pressure or of the size of the spleen.

Calorimetric researches in illnesses caused by the thyroid and the hypophyseal glands (Kalorimetrische Untersuchungen bei Erkrankungen der Schilddrüse und der Hypophyse). Baumann, C., Nederl. tijdschr. v. geneesk. **2**: 3609. 1928. Abst., Endokrinologie, **7**: 201.

In one case there was found an intense hyperthyroidism (with high metabolism) in conjunction with a bilateral ovary extirpation. In many doubtful cases calorimetry serves as a diagnostic adjuvant between hyperthyroidism and vegetative neuroses. The investigations of the hypophysis are not finished at

the present time. Of three dystrophic patients (D. adiposa genitalis), two gave normal metabolic rates, while the third patient had a lowered rate of heat production. It is well known that the basal metabolism increases with the various kinds of nutrient material used, especially with proteins, an increase not explainable by the mechanical work of the test person or by the specific dynamic action of the food. While one of the three cases with an approximately normal basal metabolism offered no trace of a specific dynamic effect, the second case (also with a normal basal metabolism) which had been treated for three months with a whole gland pituitary preparation showed a distinct specific dynamic action. In the third case, in which an anterior lobe preparation was taken for two months, the basal metabolism rose gradually and at the end the specific dynamic action was absolutely normal. The author interprets this to signify that the anterior lobe favorably influences the specific dynamic action. In conclusion: as a test method for determination of the function of the hypophysis in intracranial processes the metabolic rate together with x-ray examinations is recommended; it is also recommended for estimating the results of medical therapy in hypo- and hyper-thyroidism, and also perhaps for the determination of possible differences between constitutional psychotic processes.—J. Gagnon.

Pathogenic relation of the nervous system and the endocrine glands (Sur les affections des centress nerveux en relation avec les troubles des glandes endocrines). Bregman, L. E., Rev. franç. d'endocrinol. **71:** 353. 1929.

Since glandular function is at least somewhat controlled by the nervous system, and since the nervous system is affected by glandular products, malfunction of one produces disturbances of the other. Various endocrinopathies are studied in relation to the nervous system.—B. C.

The use of thymophysin for weak pains in the first and second stages of labor. Jarcho, J., Am. J. Obst. & Gynec. **19:** 81. 1930.

The author reports results in 18 cases studied by him and reviews reports from various European clinics that indicate the value of thymophysin (a combination of thymic and pituitary extracts) to increase the force, frequency and duration of feeble labor pains, especially during the first stage but also in the second stage when the pains have stopped. The preparation is administered intramuscularly, preferably in the gluteal region. It seems best to begin with a dose of 0.5 cc., followed by a second of 1 cc., if the first does not prove effective. Thymophysin not only hastens and facilitates normal delivery by aiding dilatation of the passages but also lasts into the third stage, so as to promote expulsion of the placenta. The most favorable type of case is primary inertia. When the uterine musculature is exhausted by prolonged labor, the preparation proves ineffective. In such cases, the mother should be given a rest before labor is resumed. Then the thymophysin may prove of value. It does not appear to injure the mother or child. Results are sufficiently encouraging to justify other physicians having the facilities to employ the preparation and observe their results. In the meantime, final judgment as to its value should be withheld.—R. G. H.

The sexual effects of non-genital endocrine glands. The virilizing action of substances of cortico-adrenal and hypophyseal origin (L'influence sexuelle des glandes endocrines non-genitales. L'action virilisante de la substance cortice-surrenale et de l'hypophyse). Marañon, G., Rec. franç. d'endocrinol, **8:** 1. 1930.

Hormonal influences on sexual evolution are of two sorts, gonadal and extragonadal. Of the latter there are again two kinds, one of which seems active for sexuality in both sexes, the other is specific for one or the other sex. The adrenal and hypophysis produce substances of a virilizing type, which seems to be independent of their other hormonal effects.—B. C.

Studies on capillaries in diseases of the nervous system and glandular internal secretion (Recherches de capillaroscopie et des troubles vasculaires dans quelques maladies nerveuses et des glandes a secretion interne). Marinesco, G. and A. Bruch. Presse méd. **38:** 665. 1930.

Marinesco and Bruch report their studies on capillaries in diseases of the nervous system and glandular internal secretion. They say that the contraction of the capillaries is controlled by the vasomotor nerves and the contract-

ing Rouget cells of the capillaries. The authors report from studies of nervous maladies and glands of the internal secretion. They believe that studies of the size and type of capillaries are useful in a diagnostic way. They report their findings on the capillaries in various nervous affections such as polyneuritis of arsenical origin, wounds of the brachial plexus and in hemoplegia. In the latter condition the capillaries are definitely dilated and tortuous, and they report also in regard to the studies of the capillaries in endocrine disorders. Studies of the capillaries are given in cases of myxedema, Simond's Disease and acrocyanosis, likewise in abiotrophic disturbances. They report a case of Charcot-Marie type of amyotrophic sclerosis and achondroplasia. Several figures illustrating the various capillary findings in these diseases accompany the article.—Robert C. Moehlig.

Endocrines and digestive disorders (Les troubles endocriniens dans, les maladies de l'appareil digestif). Moutier, F., Rev. franç. d'endocrinol, **8**: 115. 1930.

A summary of various digestive syndromes, occasioned by or concomitant with endocrine disturbances. The author suggests that if one could remove the exaggerations and sometimes far-fetched theoretical deductions relative to endocrines, the relation of these glands to digestion would form an interesting chapter in modern pathology.—B. C.

Roentgenographic studies in normal osseous development. Shelton, E. K., J. A. M. A. **96**: 759. 1931.

An important study that should be consulted in the original, since it does not lend itself to further condensation. The action of various endocrine factors is discussed.—R. G. H.

Hereditary progressive primary myopathy (Myopathie primitive progressive a type familial). Vermeylen, G. and Minne, J. de neurol. et de psychiat. **30**: 334. 1930. Abst., Rev. belge sc. méd. **2**: 869.

In this case the illness was transmitted every second generation to the males through the female line. The etiology of the disease could not be discovered. From the pathogenic viewpoint a possibility of endocrine disturbance is noted as has been reported elsewhere by others. A dysfunction of the adrenal and thyroid glands was found in this case; tachycardia at rest increased by an upright posture; arterial hypotension 9:4 and a basal metabolism of —22 per cent.—J. Gagnon.

On lowering of metabolism by use of Lugol's solution (Comment abaisser le metabolisme a l'aide de la solution de Lugol?). Bernard-Delcourt, E., Rev. belge sc. méd. **2**: 46. 1930.

Confirming the previous researches of Dautrebande, and Dautrebande and Lemort, on the method of action of Lugol's solution in hyperthyroidism of whatever character, the authors affirm that Lugol's administered according to the doses, whether small and increasing or fractional and very small, or fractional and increasing, can be adapted to the most varied reactional possibilities of the thyroid gland. The small fractional doses (Type II) are a valuable method for quickly changing the direction of the iodine treatment. They cause a quick lowering of the basal metabolism and rearrangement of the dosage is of value. It seems, as Dautrebande has shown, that certain cases demand this type of iodine distribution to any other. It is necessary to consider this and the taking of frequent metabolic rate determinations (preferably every day) in order that the pre-operatory treatment from the start may be directed in a favorable manner to adapt it strictly to the circumstances and to the thyroid reaction.—Author's Summary.

Human ovarian tumor with virilizing effect on bearer. Berner, O., Norsk mag. f. laegevidensk. **91**: 1177. 1930. Abst., J. A. M. A. **96**: 648.

Including Popoff's case, Berner's makes the sixth case of testicular tubular adenoma of the ovary reported in the literature. As in the cited cases of Pick, Schickele, Neumann and Strassmann the testicular portion of the tumor was sharply defined from the ovarian and of the same yellow color as the testis

parenchyma, and the smaller, ovarian portion of the tumor rests almost like a hood on the testicular portion. The signs of hermaphroditism in this instance gradually disappeared after excision of the ovary. He is inclined to ascribe the testicular part of the tubular adenoma to a shifting in the person's chemical milieu.—Author's Summary.

Does the thyroid gland play a part in the modifications of the ovary and the genital tract of the immature rat caused by the injections of urine of pregnant women? Bourg, J., Compt. rend. Soc. de Biol. **104**: 105. 1930. Abst., Rev. belge. sc. méd. **2**: 653.

The daily injections of 0.5 to 0.7 cc. of the urine of pregnant women during the first four months of pregnancy into immature rats and mice produces modifications of the histological structure of the thyroid corresponding to a greatly increased secretory activity comparable to that which is obtained after injection of extract of the anterior lobe of the hypophysis. But the thyroid does not intervene in the production of the ovarian reaction appearing after hypophyseal implantation or injection of urine of pregnant women, since these two treatments administered to the immature thyroidectomized mice and rats produce the same effects as in normal animals, that is, enlargement of the follicles, hypertrophy of the internal theca and the tubes, the disappearance of the fatty prepuberal borders of the uterine epithelium, the keratinisation of the vaginal epithelium.

Comparative study of the testicles and ovary of the immature rat treated with the urine of pregnant women obtained during the first four months of gestation. Bourg, J., Soc. belge de Biol. **104**: 107. 1930. Abst., Rev. belge sc. méd. **2**: 654.

The injection for 5-10 days of 0.7 cc. of urine, obtained during the first four months of human pregnancy, into immature male rats 30 days old causes in the testicular region a hypertrophy of the interstitial tissue without modification of the seminferous tubules. This reaction is similar to that observed under the same conditions in immature female mice in the ovarian interstitial tissue, particularly the internal theca.

The histological modifications of the genital tract of immature male rats treated with pregnant women's urine of the first four months of pregnancy. Bourg, J., Soc. belge de biol. **104**: 109. 1930. Abst., Rev. belge sc. méd. **2**: 654.

The injection for 10 days of 0.7 cc. of the urine of pregnant women, obtained during the first four months of pregnancy, into immature male rats or mice about 30 days old caused the appearance of the following modifications: (1) a considerable hypertrophy of the epididymus with the enlargement of the tubes, whose cells become larger; thickening of the muscular walls and numerous mitoses; (2) in the vas deferens, epithelium greatly raised, hypertrophy of the muscular walls and widening of the opening; (3) in the seminal vesicles an abundant secretion into the orifice; the epithelium rich in mitoses and large cellular elements full of cytoplasm; (4) in the prostate region, epithelium much raised, numerous mitoses, very abundant secretions; (5) around the prepucial glands, hypertrophy with abundant secretion. The testicles are equally hypertrophied as the author has shown before, and as the various modifications described above do not appear in castrated animals it is logical to concede that they are produced through the agency of the interstitial glands of the testicle activated by the specific substance from the urine of the pregnant woman.

Comparison of the modifications of the ovaries of the immature mice and rats in the Zondek reaction (Les modifications comparées de l'ovaire dans la réaction de Zondek chez la souris et le rat impubères). Bourg, R., Compt. rend. Soc. de biol. **104**: 92. 1930. Abst., Rev. belge sc. méd. **2**: 815.

Bourg has compared the effect of injection of urine of pregnant women (Zondek-Aschheim test) on the ovary of immature rats and mice. After four injections of 0.5 cc. of urine, the ovary shows numerous enlarged follicles, some of which are hemorrhagic, and numerous hypertrophied atretic follicles with corpora lutea completely absent. In the impubered rat under the same conditions there is seen a small number of hypertrophied atretic follicles, with

no trace of hemorrhagic follicles, formed by a considerable proliferation of the internal theca; this thecal hypertrophy, in contrast to what is observed in the mouse, appears equally around the normal follicles and the young follicles. The thecal formations, in both the rat and the mouse, are rich in fatty spots, easily stained by Sudan III. This remarkable secretory activity, started by the injections of urine from pregnant women and maximal after five daily injections, diminishes if the injections are continued.—J. Gagnon.

Folliculin and periodicity of sexual cycle (Ciclo sexual periodico y foliculina). del Castillo, E. B. and C. J. Calatroni, Rev. Soc. argent. de biol. **6:** 108. 1930. Abst., Physiol. Absts. **15:** 543.

Daily injections of 0.1 to 2 units in rats were made during several months. A latent period, summation of effect, after-discharge, and tendency to periodicity more marked with time were observed. Ovary and corpus luteum are therefore not indispensable for periodicity of cycle. Uterus and vagina have a periodic activity, autonomous or governed by an unknown factor, which is made manifest by the presence of folliculin.

Modifications of the ovary of the white rat treated with thyroid extract (Modificazioni dell'ovario dei ratti albini tratti con estratti tiroidei). Dulzetto, F., Arch. de biol. **40:** 227. 1930. Abst., Rev. belge sc. méd. **2:** 654.

The author has followed the histological modifications observed in the ovaries of white rats undergoing thyroid treatment; the thyroid extract was injected subcutaneously daily into young females 20-25 days old and weighing 25-30 grams at the beginning of the experiment. The first effect observed consisted of a reduction of the number of primordial follicles. Modifications of the granular cells are observed at the same time that a very early appearance of the follicular liquor occurs. Moreover, it can assist in a degeneration of the cells of the granular layer; this affects the peripheral parts at first, then proceeds on to the central parts, finally causing the breaking up of the egg. The author regards these phenomena as representing the follicular evolution following a greatly accelerated rhythm. The follicles which degenerate most easily are those whose evolution was most advanced at the beginning of the thyroid injections. The physiological consequence of this treatment is the lessening of the number of ovules which can be fertilized; this is verified by a smaller birth rate in the treated females than in normal females. In these experiments it should be stated that the number of females born remained constant, while the number of male births was diminished.

The quantitative assay for the testicular hormone by the comb growth reaction. Gallagher, T. F. and F. C. Koch, J. Pharmacol. & Exper. Therap. **40:** 327. 1930.

Data are given to show that an assay over a period of five days is the optimum time for assaying the testicular hormone. The range of variation in response to variations in dosage is studied and from these data a curve of variation in growth in response to dosage is given. Using this curve, various unknowns have been assayed with satisfactory results. From this work a bird unit is defined as "that amount of hormone which, when injected daily for five days, yields an average of 5 mm. increase in length and height of the combs of at least five Brown Leghorn capons."—T. F. Gallagher.

The sex hormones. Hoet, J. and J. Schockaert, Rev. belge sc. méd. **2:** 780. 1930.

A review of recent literature with excellent bibliography.—R. G. H.

The relationship between basal metabolism, alkaline reserve and uric acid content of the blood in endocrine and metabolic illnesses (Das Verhältnis Zwischen Grundumsatz, Reservealkalinität und Harnsäuregehalt im Blute bei Endokrinen- und Stoffwechselkrankheiten). Kalnin, A., Russian J. Endocrinology, **1:** 115. 1930.

From the results obtained from 15 endocrine and 22 metabolism patients in which the basal metabolism was determined by Krogh's apparatus, the alkaline reserve by Van Slyke's method, and the uric acid by Benedict's procedures, Kalnin concludes: that the basal metabolism determination is very valuable in

hyperthyroidism, since in most cases the increase in metabolism runs parallel with the severity of the illness; that in hyperthyroidism the majority of cases have acidosis or an inclination to acidosis, in only a minority of cases is the acid-base equilibrium in the normal value, and very seldom is it alkaline; that gout can be observed without an increase of the uric acid content of the blood since the severity of the illness cannot be judged by the quantity of uric acid present; that the uric acid content of the blood can undergo marked lessening, or an increase of it can be shown in obesity and arterio-sclerosis.—J. Gagnon.

Hormones in invertebrates (Die Innere Sekretion bei Wirbellosen Tieren). Koller, B., Biol. Rev. **4**: 269. 1929. Abst., Physiol. Abst., **15**: 538.

The presence of active sexual hormones in insects can be assumed with a reasonable degree of certainty in cases where parasitic or experimental castration brings about specific changes in secondary sexual characters (instance, rhizocephalic castration of decapod crustacea). Stylopisation in hymenoptera and the destruction of lumbriculid testes by parasites show this. Experimentally it has been definitely shown that the formation of the brood pouch in Asellus is dependent on the possession of functional ovaries. In Physcosoma the presence of an endocrine gland essential for the life of the animal has been demonstrated. Certain tissues of cephalopods are histologically suspect as endocrine in function, and there is evidence that hormones are produced by the oenocytes of larval and adult insects, probably in connection with ecdysis and pupation. The chromatophore action of shrimps and prawns is undoubtedly endocrine, as is the colour change of Dixippus and related aquatic coleoptera.

The effect of cryptorchidism and of castration on the chemical composition of rats. Korenchevsky, V. and M. Dennison, Biochem. J. **24**: 954. 1930.

The experiments were performed on 46 rats. A method was used for the investigation of the chemical composition of small animals, which gives approximate but accurate data. This method was applied for ascertaining the content of water, solids, nitrogen and fat in castrated and one-sided and both-sided cryptorchid male rats, as compared with that of normal litter male animals. The amount of intra-abdominal fat was increased in both cryptorchid and castrated animals, but to a greater degree in the latter. The nitrogen content was slightly decreased in both-sided cryptorchid and in castrated rats. This decrease, however, is chiefly due to the increased proportion of fat in the bodies of cryptorchid and castrated rats, and, therefore, is not due to the impoverishment of the bodies of these animals in nitrogenous substances. A slight increase in the content of solid matter was found in both-sided cryptorchid and in castrated rats. This increase can be explained by an increase in the deposition of fat and probably also of nitrogenous substances.

—V. Korenchevsky.

Reaction of the seminal vesicles and of the testicles of white mice after injections of urine of men and of pregnant women [Réactions des vésicles séminales et du testicule (souris blanche) après injections d'urine de femme gravide et d'urine d'homme]. Laurent, G., Compt. rend. Soc. de biol. **104**: 115. 1930. Abst., Rev. belge sc. méd. **2**: 816. 1930.

The author's observations show that the individual variations of the seminal vesicles of the impuberal male mice are too extensive to be of use as a test for microscopic examination after the injection of urine of pregnant women. The microscopic examination, on the contrary, gives more certain and regular indications. The urine of men injected for 10 or 15 days causes a greater hypertrophy of the interstitial tissues than the urine of pregnant women, but the latter causes a greater division of the epithelial cells of the vesicles.—J. Gagnon.

The cyclical changes in the human vagina (Zur frage der cyklischen Veränderungen der menschlichen Scheide). Lindemann, R., Ztschr. f. mikr. Anat. Forsch. **13**: 373. 1928.

Forty histological sections of human vaginal mucosa from sexually mature women are studied to determine if there are any cyclical changes in the epithelium. In this series of sections there is at least one section from each of the 28 days of the menstrual cycle. Three types of vaginal mucosa are described. In the first the epithelium consists only of a basal layer; in the

second it is composed of the basal layer and a superficial lamellated layer; in the third type there are the basal and superficial lamellated layers with an intermediate cornified zone. Each of these types of vaginal epithelium is found in all the phases of the menstrual cycle. They also occur in the presence of physiologic amenorrhea—as during pregnancy and after the menopause. The conclusion is reached that there is no relation between the changes in the histology of the vaginal epithelium and the phase of menstruation.

—M. R. White.

Production of ovulation during pregnancy (Künstliche Ovulation während der Schwangerschaft durch Hypophysenvorderlappen). Loeser, A., Klin. Wchnschr. **9**: 1855. 1930. Abst., Physiol. Absts. **15**: 667.

A powder prepared by acetone treatment of the pituitary anterior lobe was used. This was rubbed up in saline and injected intramuscularly into pregnant rabbits. The animals were killed 70 hours later. The ovaries contained several ripe follicles, and serial sections revealed an ovum in the Fallopian tube.

The relative amounts of oestrin required to produce the various phenomena of oestrus. Marrian, G. F. and A. S. Parkes, J. Physiol. **69**: 372. 1930.

The authors pointed out that the oestrin unit does not necessarily correspond to oestrin production in normal animals since standardization depends on cornification, hence the amount in the unit is too small. The present investigation is designed to determine the relative amounts necessary to produce uterine changes and copulation in ovariectomized mice. Four hundred units were required for complete uterine distention; 200 units were necessary to produce copulation in more than 50 per cent. From these results it is suggested that the 200 units is the physiological dose and that this amount is produced by the normal mouse at each oestrous. Therefore the amounts found in the urine during pregnancy are physiological. Also, it is suggested that the small amounts administered clinically can give no satisfactory results; it is estimated that the average woman would require 400,000 mouse units for analogous results—C. I. R.

Rat seminal-vesicle cytology as a testis-hormone indicator and the prevention of castration changes by testis-extract injection. Moore, C. R., W. Hughes and T. F. Gallagher, Am. J. Anat. **45**: 109. 1930.

Removal of the testes in the white rat produces marked changes in the microscopic structure of the seminal vesicles within a period of twenty days. The more apparent cytological changes are: (a) loss of secretion granules within two or three days; (b) progressive involution of the secretory epithelium; (c) severe reduction approaching total loss of the Golgi apparatus. The purified lipoid fraction of fresh bull testes dissolved in olive oil and injected subcutaneously has been found to successfully substitute for the testis in the control of the seminal vesicles. It prevents the appearance of invariable castration effects after testis removal. It rebuilds a castrate seminal vesicle of months' standing after testis removal. It serves to differentiate arrested embryonic vesicles of prepubertal castrates and brings them to functional (secretory) maturity within short periods of time. The effects of the injections are parallel to the concentration of lipins in the extracts injected. The injections must be continuous: a two- or three-day lapse allows castration changes to appear. Since a given sample entirely supplants the internal secretion function of the testis as this is indicated by the spermatozoon motility test, the electric ejaculation test, the prostate-cytology test, and the seminal vesicle-cytology test, the conclusion that the extracts contain the testis hormone or hormones appears justified.—Authors' Summary.

On the inactivation by proteolytic enzymes of the pituitary hormone extracted from the urine of pregnancy (Uber die Inaktivierung des aus Schwangerenharn gewonnenen Hypophysenvorderlappenhormons durch proteolytische Enzyme). Reiss, M., A. Schaffner and F. Haurowitz, Endokrinologie, **8**: 22. 1931.

It was found that the hormone was destroyed by activated trypsin and by true proteinase but was resistant to a protamine splitting enzyme. It was also not destroyed by pepsin in solution of pH. 3-4. It seems that the anterior pituitary hormone is more nearly like a true protein than a polypeptid.

—R. G. H.

Action of the anterior pituitary lobe on respiratory metabolism and glycogen of white mice (Acción del lóbulo anterior de la hipófisis sobre el metabolismo respiratorio y el glucógeno de la rata blanca). Artundo, A. and P. Mazzocco, Rev. Soc. argent. de biol. **6**: 391. 1930.

Intraperitoneal injection of 3 fresh homologous anterior pituitary lobes suspended in 1 cc. saline was made. No uniform variations in basal metabolism, hepatic and muscular glycogen were seen. The glycemia showed a slight tendency to decrease.—J. F. Lewis.

Hypophysis and growth (Hypophyse und Wachstum). Bauer, J., Wien. klin. Wchnschr. **9**: 625. 1930. Abst., Endokrinologie **7**: 387.

The clinical and experimental observations on the relationships between the hyophysis and growth are reviewed in a clear and comprehensive manner. Deficiency of the anterior lobe of the hypophysis produces dwarfs in animals and humans. In the rat this cannot be compensated for by commercial preparations of the anterior lobe but only by daily implantations of anterior lobe. By artificial hyperpituitarism giant rats can be produced, while the symptoms of acromegaly have been produced in a bulldog by Putnam, Benedict, and Teel. We must admit there are several hormones in the anterior lobe of the hypophysis, to wit, beside the growth hormone, the two sex hormones (prolan A and B) and perhaps also a metabolic hormone. The hypophysis regulates the fundamental growth and development in the genotypic plan. Frequently it is affected only by disturbances in the course of constitutional diathesis. Often growth derangements appear in a family in varying extremes. There are observations reported of an eunuchoid giant, whose grandfather was likewise a giant, and of a chondrodystrophic dwarf in a gigantic family. Relations are indicated between immoderate functioning of the anterior lobe of the hypophysis and tumor formation.—J. Gagnon.

Action on intestine of vaso-pressin and oxytocin treatment of ileus paralyticus [Die Wirkung des vasopressins und Oxytocins auf die Darmperistaltik und die Behandlung dar Darmlahmungen (Ileus paralyticus) mit Vasopressin]. Elmer, A. W., L. Ptaszek, and M. Scheps, Klin Wchsnchr. **9**: 1765. 1930. Abst., Physiol. Albsts. **15**: 584.

Vaso-pressin in the rabbit augments intestinal movements and oxytocin depresses them. Vaso-pressin is more active in stimulating the intestine than pituitrin, owing to the presence in the latter of oxytocin. Cases are described in which vaso-pressin was used with good effect in the treatment of paralytic ileus.

The diencephalo-hypophyseal system in sleep (Il sistema diencefalo ipofisario nel sonno). Florence, A. S., Riv. di pat. nerv. **35**: 72. 1928.

The author believes there is an interrelation between the infundibulum, the centers of the third ventricle and the hypophysis. According to him sleep is induced by vaso-constriction of the vegetative centers brought about by direct influx of pituitrin.

The significance of anterior pituitary hormone in the blood of gynecologic patients. Fluhmann, C. F., Am. J. Obst. & Gynec. **20**: 1. 1930.

The presence of large amounts of the anterior pituitary sex hormone (or hormones) in the blood is readily determined by a method based on the Aschheim-Zondek "pregnancy test," and the results of the examination of 319 patients are reported in this study. The test proved negative under the following conditions: (a) At any stage of the cycle in women with a normal menstrual history; (b) In patients less than forty years of age with anatomic pelvic lesions, such as carcinoma cervicis uteri, fibromyoma uteri, pelvic inflammatory disease, glandular hyperplasia endometrii, etc.; (c) In patients with "hypo-ovarian" conditions, as manifested by short periods of amenorrhea, scanty regular menses, or persistently delayed menses. The patients with positive results could be classed into three categories: (a) During pregnancy, when the test is characterized by the "haemorrhagic cyst" and "luteinization" reactions; (b) In the presence of a total ovarian deficiency, when the test gave mainly the "ovulation" reaction. This group was represented by women following a complete operative extirpation of the ovaries, after radiation castration, and after the menopause. Some patients with prolonged periods of functional amenorrhea also probably belong to this category. (c) A group com-

posed of women in the early stages of the menopause with irregular profuse periods, and a small number of younger patients with irregular (too frequent) menses or severe dysmenorrhea. The test when positive showed the "ovulation" reaction. The etiologic factor is not known, but the possibility that the symptoms may be the result of a "hyperpituitary" condition must be considered.—Author's Abst.

II. Observations on the effect of pitressin on blood pressure, pulse rate and respiration in dogs. Gruber, C. M. and W. B. Kountz, J. Pharmacol. & Exper. Therap. **39**: 275. 1930.

The first intravenous injection of pitressin in unanesthetized dogs was followed in all of the experiments by a fall in arterial blood pressure (confirmation of Gruber). Similar findings were noted following the intravenous injection of pitressin in dogs under either ether or chloretone anesthesia. The normal blood pressures in twenty-four unanesthetized dogs of various weights and ages were studied. In these a wide variation was noted, the lowest being 110 and the highest 230 mm. mercury, the average being 154, the normal variation in each animal, however, being less than 10 mm. above or below the control level. In a small group of animals with both vagi cut the average was less than that noted in the normal animals. In a still smaller group with the carotid arteries tied off the average blood pressure was higher than the average found in the normal animals. In the unanesthetized dog following the injection of pitressin the heart rate at first decreases during the primary rise in blood pressure, then it accelerates during the drop in blood pressure and decreases again during the secondary prolonged rise in blood pressure. Similar findings were recorded in dogs under either chloretone or ether anesthesia. Neither the injection of atropine nor the cutting of both vagi before the injection of pitressin completely prevents the changes in cardiac rate. In the normal animal the intravenous injection of atropine after the injection of pitressin increases the rate of heart beat above the control rate. In those dogs in which the vagi were cut, atropine injected intravenously had no effect upon the slowed cardiac rate caused by the injection of pitressin. The acceleration in heart rate which occurs during the fall in blood pressure after the injection of pitressin is mainly, if not wholly, a reflex compensatory phenomenon. The sudden fall in blood pressure reflexly exciting the cardio accelerator center is an attempt on the part of the cardio-vascular system to maintain a normal blood pressure. The slowed heart rate caused by the injection of pitressin is partly a reflex due to stimulation of the cardio-inhibitory center through the depressor nerve, and partly due to a direct action upon the heart muscle itself, the latter due probably to injury through vaso-constriction of the coronaries. The secondary rise in blood pressure was higher in the dogs which had received atropine before the injection of pitressin. Likewise it was higher in those in which the vagi had been severed before the injection. It is believed that this is due to the fact that the heart rate does not slow as much in these cases following the injection of pitressin as it does in the other experiments. Ligating both carotid arteries did not change the action of pitressin upon either the blood pressure or heart rate. Ligation and excision of both adrenal bodies had no influence on the effect of pitressin upon either the blood pressure or heart rate. Pitressin, like whole extract of the posterior lobe of the pituitary, when injected intravenously in unanesthetized dogs causes a Cheyne-Stokes type of respiration.—Authors' Summary.

Some observations on the effect of pitressin upon the cardio-vascular system. Gruber, C. M. and W. B. Kountz, J. Pharmacol. & Exper. Therap. **39**: 435. 1930.

Pitressin in both acid and alkaline solutions produced vaso-constriction of the coronary vessels in excised perfused isolated hearts of rabbits (confirmatory of Anrep). Pitocin similarly injected caused coronary vaso-dilatation. The peripheral vessels of frogs were always constricted by pitressin in alkaline solution, but usually dilated when the acid solution was used. This latter action, it is believed, is due to the acidity of the fluid injected. Aqueous extracts of pure pituitary powder caused an increase in the volume of the heart (confirmation of Kolls and Geiling, and Bodo). Pitressin produced an increase in the volume of the dog's heart when injected intravenously. A second injection of either pitressin or pituitary extract subsequent to the first injection did not influence cardiac volume. In these experiments pitocin did not influence cardiac volume when injected intravenously.

—Authors' Summary.

The electrocardiogram of non-anesthetized dogs as modified by the intravenous injection of pitressin, atropine sulphate and vagus section. Gruber, C. M. and W. B. Kountz, J. Pharmacol. & Exper. Therap. **40**: 253. 1930.

In non-anesthetized dogs, pitressin injected intravenously caused very definite cardiac changes: (a) A brief period of slowing; (b) a brief period of acceleration; (c) a prolonged period of profound slowing. During this phase, electro-cardiographic curves showed shifting pacemaker, prolongation of the auriculo-ventricular conduction time, sino-auricular block, partial auriculo-ventricular block, extra systoles, high T-waves, high branching T-waves and bigeminal pulse. After atropine or after vagus section, pitressin produced the same cardiac changes except that the decrease in heart rate was not as great nor was the acceleration as pronounced. It appeared that in the non-anesthetized dog pitressin affected the heart (a) by reflex stimulation of the vagi through the cardio-inhibitory center; (b) by a direct action upon the heart muscle; (c) by coronary vaso-constriction producing a deficient blood supply to the myocardium.—Authors' Summary.

Further observations on the effect of pituitary extract and morphine sulphate upon excised dogs' intestine. Gruber, C. M. and G. Pipkin, J. Pharmacol. & Exper. Therap. **38**: 401. 1930.

High dilutions of pituitary extract, if effective, cause an increase in tonus and tonus oscillations in longitudinal segments of excised dogs' intestine. High concentrations of pituitary extract cause an immediate loss in general tonus and complete disappearance of the rhythmic contractions. The degree of tonus normally present in the segment before the addition of pituitary extract is a factor in the results obtained. If the tonus is high, even dilute solutions may cause relaxation, while if the tonus is low the strong solution may stimulate the gut. Morphine sulphate increases the tonus, and, in many instances, the height of rhythmic contractions, in excised segments of normal dog intestine. A similar action is noted in excised longitudinal segments taken from a Thiry-Vella loop. Papaverine antagonizes the morphine action in both types of segments.—Authors' Summary.

Concerning the hormone which causes ovulation (Über das ovulationsfördernde Hormon des Hypophysenvorderlappens und die Funktion des Corpus luteum). Haupstein, V. P., Endokrinologie, **7**: 104. 1930.

After the first oestrous caused by implantation of anterior lobe of the hypophysis in immature white mice there is an anoestrous period which extends to puberty and the more or less regular establishment of the oestrous cycle. Permanent oestrous cannot be produced in immature white mice by increasing the amount of anterior lobe of the hypophysis implanted any more than it can be effected in mature mice by implanting very great quantities of this part of the gland. From the large numbers of corpora lutea found in the ovaries of the mice used in this work it would appear that the corpora lutea exert a limiting influence upon the extent of the heat reaction. By implantation of corpus luteum tissue, whether the corpus luteum of menstruation, of pregnancy, or the persistent corpus luteum found in cattle illness, oestrous can be suppressed for a long time. This does not occur to the same degree with the tissue from very young granular glands.—J. Gagnon.

Phlorizin diabetes in hypophysectomized dogs (La diabetes floridcinica de los perros hipofisoprivos). Houssay, B. A. and A. Biasotti, Rev. Soc. argent. de biol. **6**: 326. 1930.

Hypophysectomized dogs were intoxicated with phlorizin 22 to 65 days following operation. In 3 to 9 days of intoxication 6 out of 8 died. Only 1 out of 6 controls and 1 out of 5 with lesion of the tuber cinereum had toxic symptoms and died. Hypophysectomized dogs lost less weight than the two other groups; they had no polyuria, which was marked in controls, blood sugar fell below 0.07 per cent, while only one control had a blood sugar as low as this figure. Injection of glucose did not produce complete recovery from toxic symptoms. Glycosuria was less marked, only one-third of the amount eliminated per kgm. per day by controls. Less nitrogen was eliminated by the operated dogs and the D:N ratio was lower. Animals with lesions of tuber cinereum intoxicated with phlorizin showed no difference with normal controls.—J. T. Lewis.

Functions of pituitary and infundibulum in Bufo arenarum (Funciones de la hipófisis y de la región infundíbulo-tuberiana del sapo Bufo arenarum). Houssay, B. A. and L. Giusti, Rev. Soc. argent. de biol. **6**: 206. 1930.

Insufficiency of pars intermedia produces paleness of the skin, and hyperfunction darkening. Insufficiency of pars glandularis produces (a) testicular atrophy, (b) asthenia, convulsions and death, (c) hypersensitiveness to insulin, (d) attenuation or total absence of pancreatic diabetes, (e) sometimes hypoglucemia and diminished hepatic glycogen content, (f) arrested development (in other batrachians). Implantation of pars glandularis prevents the appearance or corrects these symptoms and produces opposite ones besides ovulation and expulsion of ova. Symptoms of infundibular lesion are: (a) a bronzed epidermic cuticle, (b) polyuria, (c) reflex sexual flexion of anterior limbs even after hypophysectomy or gonadectomy. Lesion of the tuber stimulates the melanophore-dilating secretion of pars intermedia, and the secretion that provokes ovulation; it inhibits the "diabetogenic" secretion.

—J. T. Lewis.

Data on the function of the human hypophysis (Angaben über die Funktion der menschlichen Hypophyse). Janossy, J. and F. Magoss, Wien. klin. Wchnschr. **43**: 1201. 1930.

The cisterne fluid of three patients suffering from hypophyseal infantilism caused contraction of the isolated rat or guinea pig uterus even in a 1:5 dilution. In one case the effect was exactly like that of the fluid taken from a normal man and used as a control, but in the other two cases the fluid of the infantiles caused a smaller reaction. The hypophysis of an infantile patient produces such a secretion which is discharged over the infundibulum into the third ventricle of the brain, although it is admitted that this secretion production is somewhat less than that of the normal man. The authors could not demonstrate this uterus contraction principle in several experiments in which the fluid from their patients, ill with diabetes insipidus, was used. This circumstance shows that in patients with diabetes insipidus the excretory function of the hypophysis can be deranged. This disturbance is characteristic for hypophyseal diabetics alone. Since the uterus contracting material is identical with the secretion of the posterior lobe according to Trendelenburg's animal experiments, it is concluded that hypophyseal diabetes insipidus is chiefly due to dysfunction of the posterior lobe, and that the path of this secretion of the posterior lobe is over the infundibulum into the third ventricle of the brain. Formerly these facts were demonstrated in animal experiments alone, but foregoing researches show that the same circumstances exist in humans. The examination of the uterus contracting material is suitable moreover as a diagnostic method for differentiating hypophyseal diabetes insipidus from non-hypophyseal diabetes.—J. Gagnon.

Glycaemic variations with hypophysial extracts (A propos des variations glycémiques consécutives à l'administration d'extrait hypophysair postérieur). La Barre, J., Arch. internat. de Pharmacol. **38**: 409. 1930. Abst., Physiol. Absts. **15**: 661.

In animals injected with post-pituitary extracts there is a phase of hyperglycaemia followed by one of hypoglycaemia. The increase of the blood sugar following the injection is due to hypersecretion of adrenalin, and the hypoglycaemic phase is the result of increased insulin production. This increased output of insulin is not due to parasympathetic influence, but to direct action on the islets of Langerhans.

Law of follicular constancy, the law of puberty and the anterior lobe (Loi de la constance folliculaire; loi da la puberte et lobe anterieur de l'hypophysis). Lipschutz, A., Rev. franç. d'endocrinol. **8**: 97. 1930.

The law of follicular constancy is based upon the fact that unilateral, or partial castration, does not affect the number of young, or of corpora lutea, due to the hypertrophy or the remaining tissue. The law of puberty is based upon an x factor, presumably the same in both male and female, and probably originating in the pars anterior of the hypophysis.—B. C.

The Zondek-Aschheim reaction. Marsalek, J., Bratisl. lekár listy, **10**: 130. 1930.

The positive Zondek-Aschheim reaction in mola hydatidosa and chorionephithelioma, the Philipps' experiments and the success of an implantation of the chorionephithelioma with the production of a positive reaction of the hypophysis hormone support two new assertions: The hypophysis hormone during pregnancy is not only increased through the augmented activity of the hypophysis anterior lobe, but is also formed by the foetal ectoderm. The origin of the lutein cysts in chorionephithelioma must be attributable to the action of the hypophysis hormone. Practically the Zondek-Aschheim Reaction must be estimated as the most reliable reaction for the early evidence of pregnancy; in chorionephithelioma as diagnostic expedient for the early recognition of this malignant tumour after macroscopic removal, for example, of parts of the mole, as well as for the early diagnosis of metastases, which originate after the destruction of the primary deposit, whether it be after the complete destruction of the same, or with the non-active behaviour of the remains of the chorion.—Author's Summary.

Infundibulo-hypophysary dysfunction and narcolepsy (Disfunzione infundibulo-ipofisaria e narcolepsia). Pfanner, A., Riv. di pat. nerv. **35**: 80. 1930.

A case of dyspituitarism with spells of narcolepsy is discussed, and the author claims that the sleep is not induced by vasoconstriction of the centers of the third ventricle through action of the hypophysis, but through the mechanism of this gland in ruling the metabolism and the acid-base balance.—G. V.

A portal circulation from the pituitary to the hypothalamic region. Popa, G. and U. Fielding, J. Anat. **65**: 88. 1930. Abst., Physiol. Absts. **15**: 667.

A preliminary note on a portal system of veins in man. Vessels collect blood from all parts of the gland, ascend in the stalk as parallel veins, and acquire thick neuroglial sheaths. Superiorly, beneath the infundibular recess of the third ventricle, the vessels lose their sheath and open out into a network of fine vessels supported by long processes of the ependymal cells in the hypothalamus. The arterial supply to the three parts of the gland and the venous return into the cavernous sinus or via the portal system of the stalk to the hypothalamus is described. Colloid material is seen in the vessels of the portal system and among some of the cells of the hypothalamus.

Structure and function of cells of tuber cinereum (Tunzione e struttina delle cellule del "Tuber cinerum"). Poppi, U., Il Policlinico. (sez. prat.), **37**: 1382. 1930. Abst., J. A. M. A. **95**: 1950.

Poppi points out that the principal nuclei of the tuber cinereum contain a large amount of fat (consisting in part, of lipoids), which causes the displacement of the chromatic substance. These cells contain in addition numerous siderophilous granules of a lipoid nature similar to those common to the cells of the hypophysis and the suprarenals. The author recalls the researches of Abel, Collin and Sato, respectively, who found in the tuber cinereum an active principle equal to that of the posterior lobe of the hypophysis, and raises the question whether these cells have a simple reservoir function or whether they have an endocrine function of their own.

The percentage of the different types of cells in the male adult human hypophysis. Rasmussen, A. T., Am. J. Path. **5**: 263. 1929.

The results of making a differential count of the chromophobes, acidophils and basophils in 100 selected and supposedly normal male adult hypophyses from cases of sudden accidental death, in which the tissue in general was fixed within twelve hours after death, are presented. The data are based on a differential count of from 10,000 to 30,000 cells from 100 to 350 microscopic fields taken systematically from three different regions of a complete series of horizontal sections from each hypophysis. The chromophobes represent on an average 52 per cent of the total cells. They vary from 34 per cent to 66 per cent. The coefficient of variation is 15. The acidophils average 37 per cent, varying from 23 per cent to 59 per cent, the coefficient of variation being 21. The basophils strictly within the anterior lobe are the least numerous and the

most variable. The average is 11 per cent, but they range from less than 5 per cent to more than 27 per cent. The coefficient of variation is 34. Fourteen cases with a body weight 200 lbs. to 330 lbs. averaged 3.5 per cent more chromophobes and 4.6 per cent less acidophils when compared with eighty-six cases under 200 lbs. in weight. Statistically this difference is not enough to be taken seriously, although the decrease in acidophils is probably real. There is no correlation of importance between body length and percentage of any particular type of cell. Individuals over 50 years of age average nearly 4 per cent more chromophobes and correspondingly less acidophils. There is no correlation between age and basophils in the anterior lobe of the hypophysis.
—Author's Summary.

Ciliated epithelium and mucus-secreting cells in the human hypophysis. Rasmussen, A. T., Anat. Rec. **41**: 273. 1929.

Tall columnar cells with numerous delicate cilia occasionally occur in the epithelium lining the residual lumen and cysts in the region of pars intermedia of the human hypophyses that otherwise are essentially normal. Some of these cells apparently secrete a mucus-like material or undergo mucoid degeneration. There is no significant evidence that they are sensory elements. Their origin is uncertain, but probably should be looked upon as unusual differentiations of hypophyseal tissues or as migrations of nasopharyngeal elements during early stages of development. Branched tubular glands, so common in the hypophysis of young children, may be present in adults. The nature of the substance which these glands secrete is uncertain.
—Author's Summary.

Origin of the basophilic cells in the posterior lobe of the human hypophysis. Rasmussen, A. T., Am. J. Anat. **46**: 461. 1930.

A histological study of fresh normal adult human hypophyses has been made for the purpose of throwing further light on the origin of the basophilic cells that invade the posterior lobe. It appears that pars intermedia cells, both in the main stratum which forms the posterior wall of the cleft and in the strands and tubules which grow backward from it may become strongly basophilic and assume the general characteristics of basophilic cells of the anterior lobe. This transition does not involve an acidophilic stage. Only an occasional isolated acidophilic cell is found in pars intermedia. This suggests that the basophilic cells are not derived from the acidophilic type, at least under certain conditions. If these basophilic cells are the same type as the basophils found in the anterior lobe, the clear (or slightly basophilic) cells of pars intermedia might be looked upon as undeveloped cells almost exclusively of the basophilic type. While the possibility of migration of cells from the anterior lobe into the posterior lobe is not denied, it is certainly evident that abundant cells from pars intermedia may become strongly basophilic and in some instances, at least, account for the great number of basophilic cells which invade the nervous lobe.—Author's Summary.

The action of alkaline extract of anterior pituitary gland on the sex organs of the white rat (Uber die Wirkung alkalischer Hypophysenvorderlappenextrakte auf das Genitale der weiblichen Ratte). Reiss, M., H. Selye and J. Balint, Endokrinologie, **8**: 15. 1931.

Experiments were made on 9 infantile female white rats. These comprised normal controls and animals injected with alkaline hypophysis (growth) extract or sex stimulating hypophysis extract (from urine of pregnant women) singly or in combination. It was noted that the growth extract had a retarding influence on the development of the ovaries and the uterine epithelium. The luteinizing effects are to be further investigated.—R. G. H.

A propos some infundibular syndromes: diabetes insipidus and adiposo-genitalis (A propos des syndromes infundibulo-tuberiens: diabète insipide et syndrome adiposo-genital). Roussy, Mm. G., R. Huguenin and Mlle. Roques, Paris méd. **18**: 53. 1928.

The authors cite a clinical case in which diabetes insipidus and the Babinski-Frölich syndrome began suddenly, lasted 6 years, and showed an unusual intensity: a polyuria of 18 litres increasing to 43 kilograms in 8 months. They lay stress anew on the infundibular origin of similar clinical

syndromes. In their case there was no indication of intracranial hypertension and the x-rayed sella turcica was perfect. The nuclei which preside at the regulation of the diuresis, at the metabolism of the fats and at the genital functions should be neighbors and by some other remote way than the optic chiasm, as no ocular disturbance is present; and on the other hand the center of sleep ought to be more or less remote, as the latter is not disturbed. This is the least logical of hypotheses which results from this study in the absence of anatomical evidence. The polyuria was decreasing under the influence of subcutaneous injections of the posterior lobe of the hypophysis and not as the consequence of lumbar puncture. It was also lowered after a deep radiotherapy treatment.—H. G. Beck.

Influence of hormonal preparation from anterior lobe of hypophysis on various forms of hypogenitalism in men (Kann man mit Hypophysenvorderlappen den unterenturckelten männlichen Genitalapparat beim Menschen zum Wachstum anregen?). Schapiro, B., Deutsche med. Wchnschr. **56**: 1605. 1930. Abst., J. A. M. A. **95**: 1704

Schapiro describes the effects that he obtained with a hormonal preparation of the anterior lobe of the hypophysis. The preparation contained 100 rat units per ampule. It was employed on twenty-six male patients with hypogenitalism. The author classifies the patients into four groups. To the first group belong the eunuchoids of the slender type. There were six men ranging in age from 19 to 29. To the second group belong patients with genital hypoplasia, adipositas and decreased specific dynamic action. There were fifteen children ranging in age from 9 to 18 and one man aged 27. To the third group belong patients with infantilism in the sense of a generalized arrest in the development; in this group there were two children aged 14 and 18. To the fourth group belong those with cryptorchidism; in this group there were two children aged 12 and 16, respectively. Cryptorchidism was also observed in eleven cases of the first three groups. In describing the growth effects of the treatment, the author differentiates between three degrees of maturity. As the first degree of maturity he considers beginning growth of the testes and penis, increase in the pubic hair and in the axillary hair, and in cryptorchids a partial descent of the testes. As the second degree of maturity he considers complete descensus, enlargement of the testes and penis but not yet to normal size, and there is not yet a production of semen. Third degree maturity is complete sexual maturity and the presence of living spermatozoa in the ejaculate. A maturity of the first degree developed in all twenty-six cases; in fourteen instances a maturity of the second degree was noted and in nine cases a complete maturity resulted. The best results were obtained in those persons who were near the age of puberty. The hypophyseal extract also influences the gas metabolism. The specific dynamic action is increased and in most cases also the basal metabolism. It is probable that the typical slender eunuchoidism is not always primarily of a genital origin but is often due to hypophyseal disorders.

The influence of the hypophysis upon the metamorphosis of Amphibia. Schneersohn, S., J. Medico-Biologique, **5**: 85. 1929.

By means of transplantation the hypophysis of axolotls is effective in causing metamorphosis. The hypophysis of the tadpole is shown to be active even in the early stage of development before metamorphosis. The increase in the quantity of the hormone at this stage of development accelerates the metamorphosis. From the experiments with "pituitrin A" it is concluded that injections of "pituitrin A" hasten the normal metamorphosis in tadpoles and stimulate it in axolotls. There is no action of "pituitrin A" upon oral administration.—J. Gagnon.

Hypophysarian lesions and polydactilia (Lesioni pituitarie epolidattilia). Sciuti, M., Riv. di pat. nerv. **35**: 90. 1930.

A discussion of Babe's thesis that polydactilia is due to spenoidal lesions acting on the hypophysis. A case of unilateral polydactilia is presented for which a pituitary lesion is denied and the abnormality is attributed to atavic reversion.—G. V.

The use of solution of pituitary in herpes zoster. Sidlick, D. A., Arch. Dermat. & Syph. **22**: 91. 1930.

The treatment of patients with herpes zoster with solution of pituitary has much significance. Of 8,229 new patients admitted to the Jefferson Hospital Skin Dispensary from May 3, 1923, to Sept. 20, 1929, 153, nearly 2 per cent, suffered from this disease. Even in mild attacks of herpes zoster, there is discomfort; in severe cases, the extreme pain experienced by the patients often impairs their general health. Many of these persons are wage earners, and absence from their occupations complicates their economic problem. The treatment with solution of pituitary contrasted with other accepted methods of treatment has many advantages; particularly in its effectiveness in controlling pain. Pregnancy is the only contraindication to the treatment. The use of this solution was not found to be unsafe for patients with hypertension or for those of advanced age. The only untoward effect observed was a momentary sensation of faintness experienced by some of the patients.
—Author's Abst.

Action of pituicrin upon fat metabolism (First Communication). Steppuhn, O. A., A. M. Timofeewa and K. D. Ljubowzowa, Wjestnik Endokrinologii, **3**: 81. 1929. (Russian.)

In accordance with the findings of Coope and Chamberlain, the authors observed in rats after injection of pituicrin (pituitrin) an increase of the fat content of the liver which disappeared again after several hours. At the same time they stated a decrease of the fat content of the peripheral tissues which also returns again to normal conditions within a few hours. The conclusion is drawn that there takes place a wandering of fat from the periphery toward the liver during the first phase, but the amounts of fat that appear in the liver do not quite correspond with the losses of the peripheral tissues. The spontaneous restitution of a normal quantitative distribution of fat between the liver and the tissues is explained as a return of fat into the peripheral tissues. It is true that there has been observed a considerable diminution of liver sugar during the action of pituicrin, while the tissue sugar remains unchanged, but the authors do not believe that there takes place a resynthesis of fat and refilling of the peripheral tissues with fat deriving from these disappearing amounts of sugar because the fat curve and the sugar curve do not correspond exactly in time. The authors are doubtful, therefore, about the assumption of Raab that under the influence of pituicrin body fat is decomposed within the liver. The authors believe that they have solved the problem of a transformation of fat into carbohydrate in a negative sense: they could not produce any storage of glycogen in animals which had been previously depleted of glycogen through starvation by feeding them with fat while this was possible by feeding them with starch. It is true, however, that these experiments do not give any evidence concerning the question whether or not the starved organism has formed new amounts of carbohydrate out of fat and utilized them at once because in this latter case it would not have been possible to detect them by chemical means. The total amount of fat of the organism decreased during feeding with fat, while the glycogen, although small, remained unchanged.—W. Raab.

On the growth-promoting hormone of the pituitary body. Van Dyke, H. B. and Z. Wallen-Lawrence, J. Pharmacol. & Exper. Therap. **40**: 413. 1930.

The method of preparation of an extract of the anterior lobe is described in detail. The name phyone is suggested. This contains an appreciable amount of the luteinizing principle described by others in such extracts. For assay, adult normal and hypophysectomized rats were used, each receiving daily injections over three days. The maximum effect was produced 24 hours after the last injection.—C. I. R.

Syndrome of Recklinghausen, acromegalic symptoms and enormous tumor of the occipital region (Morbio di Recklinghausen, acromegalia frusta ed enorme tumore della regione occipitale). Vizioli, F., Riv. di pat. nerv. **35**: 96. 1930.

The author reports a case of neurofibromatosis with several localizations in the brain, cerebellum and hypophysis. He does not accept the theory which explains the condition as due to abnormalities of the hypophysis, since several cases of Recklinghausen's syndrome with involvement of the hypophysis never

gave a clear syndrome of acromegaly. He points out that a fibroma in the hypophysis due to neurofibromatosis is no more unusual than any other localization in the brain. In the present case the biopsy of tumor showed it to be an old fibroma in sarcomatous degeneration.—G. V.

The hypophysis hormonal (L'hemocrinie hypophysaire). Watrin, J., Rev. franç. d'endocrinol, **8**: 193. 1930.

Injections and transplantation experiments show that the anterior pituitary has to do directly with gonadal development, and producing as well a precocious development of gonadal accessory structures.—B. C.

Indications and contra-indications for insulin therapy (Indicaciones y contra-indicaciones de la Insulinoterapia). Bonilla, E., Med. ibera, **1**: 47. 1928.

The author reviews all the indications for the use of insulin. In diabetes he considers it the only specific remedy, believing that it should be employed exclusively in the light cases affected by it to attain a practically normal carbohydrate tolerance, and perhaps by its homostimulating effects to produce a regeneration of the pancreas. In illness the indications for the use of insulin can be divided into emergency, necessity, and convenience. In small and periodical doses it is very useful in the pre-diabetic conditions, being able to serve as a prophylactic in a certain way for confirmed diabetes. As to these non-diabetic diseases he believes that the processes in which insulin is truly indicated are the conditions of malnutrition and very especially infantile atrepsia; hyperthyroidism, arteritis, and dermatosis connected with a disturbance of hydro-carbon metabolism. As a single contra-indication he considers suprarenal insufficiency because of a lack of defensive mechanism against hypoglycemia.—Author's Abst.

Pancreatitis complicating mumps. Brahdy, M. B. and I. H. Scheffer, Am. J. M. Sc. **181**: 255. 1931.

Pancreatitis as a complication of mumps has been reported mainly in the French literature. During 1929 there were 6523 cases of mumps in New York City, of which 306 were hospitalized. Of the 252 cases admitted to the Parker Hospital, 13 had pancreatitis and only one of these had any other complication. All of the patients recovered completely. The onset is between the fifth and eleventh days of illness. The symptoms were nausea, anorexia and fever. The pulse was slow in relation to the temperature. The abdominal pain was in the epigastrium in most instances. Vomiting occurred frequently but there was no diarrhea.—E. L.

Insulin therapy in emaciation following calculous cholecystitis. Ceccarelli, D. Policlinico, **37**: 1665. 1930. Abst., J. A. M. A. **96**: 646.

Ceccarelli, after a short survey on insulin treatment in emaciation states in general, reports a case of marked emaciation (loss of weight 20 kgm.) following cholelithiasis, in which insulin (20 units per day in two doses) was administered. The surprising outcome (gain in weight of 17.8 kgm.), with a return of general conditions almost to normal, induces the author to advise insulin treatment in such emaciation states.—Author's Summary.

On the nervous control of insulin secretion. Hoet, J. and H. Ernauld, J. Physiol. **70**: 1. 1930.

Rabbits under anaesthesia from allylisopropyl barbiturate of diethylamine, which does not alter glucemia, were used. Injection of glucose produced hyperglucemia. After bilateral vagisection similar injection did not produce this effect. After removal of the kidney, and vagisection, the hyperglucemia persisted for hours due to failure of the pancrease to respond by insulin output. Therefore, insulin secretion depends on vagus stimulation. In vagotomized cats the increase in muscle glycogen after glucose injection did not occur.—C. I. R.

Diabetes and pregnancy (Diabetes y embarazo). Izquierdo, J. J., Arch de med., cir. y espec. **31**: 313. 1929.

During pregnancy it is necessary to distinguish true diabetes from extra-insular glycosuria, due probably to a glycogenic insufficiency of the liver combined in some cases with a lowering of renal threshold. At times it is difficult to establish a differential diagnosis and in doubtful cases it should always be treated as diabetic coma. The problem of maternal and foetal death has been reduced in a remarkable fashion by the use of insulin. On the other hand the author insists on the influence of the pre-diabetic state upon the sex life of the mother because it has been observed repeatedly that a state of hyperglycemia without glycosuria produces repeated abortions. In the diabetes of pregnancy there is a considerable tendency to acidosis caused by a diminution of the glycogenic reserves of the liver, and of circulating glucose. For this reason insulin alone will not avoid acidosis but will increase it unless abundant quantities of carbohydrates are administered at the same time. Regarding obstetrical practice, insulin should never be given at the time of labor. However, if coma occurs at the beginning of uterine contractions, as may happen in cases not properly attended during gestation, it is necessary to rapidly combat acidosis, administering greatly increased quantities of glucose with large doses of insulin.—E. B.

A circulation hormone in the pancreas (Der Nachweis eines Kreislaufhormons in der Pankreasdrüse). Kraut, H., E. K. Frey and E. Werle, Ztschr. f. phys. Chem. **189**: 97. 1930. Abst., Physiol. Absts. **15**: 580.

Extracts of pancreas were found to contain a substance having a powerful effect upon the circulation and distribution of blood. Extracts of other organs gave only traces of this effect. The substance in question in the pancreas agreed in its properties (dialysability, precipitation, etc.) with the substance previously found in blood and urine to have a similar effect on the circulation. The pancreas contains many times the amount daily excreted in the urine. It seems probable that the pancreas is the place of origin of this hormone.

The effect of insulin on the voluntary activity of the white rat. Levin, J. J. and L. B. Nice, Proc. Ohio Acad. Sc. **8**: 414. 1930.

The experiment was begun in 1927-1928 to determine the effect of subcutaneous injections of unit doses of insulin given daily, on the voluntary activity, growth and blood count of white rats. The experiment was repeated with a second set of animals in 1929-1930. The first group of rats consisted of 9 controls and 9 experimental animals which were injected daily with 1 unit of insulin. The second group consisted of 22 animals which were injected during twenty-day experimental periods with 1 unit of insulin daily. Blood counts were recorded, before and after insulin administration, for a period of 10 days. The weights were recorded in both groups of animals. In the first group the experimental animals showed an increase of 25.3% in voluntary activity over controls, while the second group showed an increase of 23.4% over the control period. The experimental and control animals increased in weight at approximately the same rate. There was no increase in erythrocyte count following a ten-day period of insulin administration.—Authors' Abst.

Action of insulin on gastric secretion (Uber die Wirkung des Insulins auf die Magensekretion). Meyer, P. F., Klin. Wchnschr. **9**: 1578. 1930. Abst., Physiol. Absts. **15**: 582.

The investigation was made on 50 cases, using the fractional method. Injection of about 20 units of insulin usually causes a rise in the acidity after 75 to 90 minutes, and a marked increase in the quantity of gastric juice secreted. The rise in secretion occurs in the hypoglycaemic phase of insulin action. Diabetics do not exhibit a gastric response to insulin unless they become hypoglycaemic. In cases of anacidity, but not complete achylia, insulin acts like histamine, causing a secretion of acid.

Oral administration of insulin to children with diabetes mellitus (Erfahrungen mit peroralem Insulin bei kindlichem Diabetes mellitus). Ottow, M., Münch. med. Wchnschr. **76**: 1584. 1929.

The question of insulin therapy in children with diabetes mellitus is of great importance when the child passes from clinical treatment into the hands

of the mother. Oral administration would be a safer and more humane method of treatment. In the two cases reported the results were striking. One child 14 years old had a urinary sugar of 18 gms., acetone bodies, and blood sugar of 177 mgm. Under diabetic standardization the acetone bodies and urine sugar disappeared but the blood sugar remained high. Ten units of insulin twice given by mouth brought the blood sugar to its normal value. The second child, 15, was severely diabetic with urine sugar 50-90 gms., acetone, and blood sugar 200. Oral administration of insulin, 75 and later 100 units, was tried. After a few days it was possible to reduce the insulin to 40 units and to increase the carbohydrate of the diet from 24 to 50 gms. The urine remained sugar free and hyperglycemia was absent. The author feels these results indicate an increase in sugar tolerance. He is also convinced that after more experimentation such a method of treatment will have an important place in the treatment of diabetes mellitus in children.

—Estelle Hawley.

Existence in insulin of a 2 thiol-imidazol group [Contribución al estudio de la constitución química de la insulina (segunda comunicacion). Sobre la posible existencia de un grupe 2 thiol imidazol en la molécula insulínica]. Ruiz, C., L. Silva and L. Libenson, Rev. Soc. argent. de biol. **6**: 198. 1930.

The following substances had no hypoglycemic activity: Methyl-2-thyolimidazol; 4-5 amino-methyl-2 thyol imidazol II; 2 thyol 4 or 5 gluc imidazol III; 2 thyolimidazol V. Hypoglycemia is produced by 4 or 5 methyl-2 thyolimidazol.—J. T. Lewis.

Diabetes mellitus in infant eleven months old. Shelley, E. G., Pennsylvania M. J. **34**: 256. 1931.

The case reported occurred in a male infant 11 months old whose birth was normal and who was perfectly well until 8 months of age when he was ill for several days with chill and fever which the mother attributed to teething. He recovered from this but was fretful thereafter. At 9 months there occurred an undetermined fever of 4 days' duration. At 10 months polyuria, polydipsia, polyphagia, itching of the skin and sweating of the head was noticed. At 11 months glycosuria was first discovered and the child was admitted to the hospital. The blood sugar on admission was 259 mgm. per 100 cc., the urine contained 2 per cent of sugar and a trace of acetone bodies. A few days later the blood sugar was increased to 327 mgm. As a result of dietary and insulin treatment the symptomatology improved somewhat and the general body nutrition was maintained. However, the high blood sugar content persisted and urinalysis always revealed large amounts of sugar. At 15 months of age the child was taken acutely ill with fever, vomiting and diarrhea, which proved fatal in 2 days. It so happened that all the other members of the family were ill with gastro-enteritis which was epidemic in the community at that time. The author presents this case because of its rarity and the unusual feature which consisted in the maintenance of good nutrition in the presence of a severe diabetic status.—I. B.

Postoperative parathyroid insufficiency. Boothby, W. M., S. F. Haines and J. De J. Pemberton, Am. J. M. Sc. **181**: 81. 1931.

Three cases are reported and recent literature is reviewed. It is calculated that in acute postoperative parathyroid insufficiency the tetanic spasms, including laryngeal spasm, can be controlled by the administration of a generous teaspoonful of powdered calcium lactate dissolved in water every two hours. In the severe cases in which the patients have difficulty in swallowing, 5 or 6 additional teaspoonfuls of calcium lactate are dissolved and given by proctoclysis. Only rarely will it be necessary to give calcium chlorid intravenously. Also in the immediate postoperative period it will hardly ever be necessary to give parathormone. In the milder cases of chronic postoperative parathyroid insufficiency (in some of which insufficiency probably is not complete) the condition can sometimes be controlled by the regular administration, four or five times a day, of 1 teaspoonful of calcium lactate dissolved in water, aided by the administration of 2 or 3 teaspoonfuls of cod-liver oil daily. Irradiated ergosterol can be used instead of cod-liver oil, although as yet the dosage advisable for longer periods is not determined. In the more severe cases, including those in which insufficiency apparently is complete, parathormone must also be administered. As in all deficiency diseases, medication

must be continuous and regular, and in the presence of complete deficiency it must probably be administered indefinitely. In general, it has been found that for continuous administration only small doses should be used, such as 5 units of parathormone daily, or 10 units every other day. Sometimes 10 units every day, and occasionally for short periods, 20 units daily will be needed; the use of larger doses over any considerable time is probably dangerous. On a regimen of calcium lactate, cod-liver oil or irradiated ergosterol, such as has been outlined, even patients with severe and apparently complete parathyroid insufficiency can be maintained in good, if not perfect, health. If the parathyroid insufficiency is less severe and apparently not complete, the patient can be maintained in good condition without parathormone if suitable doses of calcium lactate and cod-liver oil or irradiated ergosterol are administered.—Authors' Summary.

Postoperative parathyroid insufficiency. Boothby, W. M., S. F. Haines and J. de J. Pemberton, Am. J. M. Sc. **181**: 81. 1931.

Following 13,300 thyroidectomies, parathyroid insufficiency was noted in 88 females and 1 male. In 44 of these cases the insufficiency was chronic and 6 of them were complete insufficiency. The postoperative treatment instituted as soon as any symptoms were observed was the administration of 30 grains of calcium lactate by mouth every two or three hours. Some of the patients complained of a tingling and numbness of the fingers before Chvostek's and Trousseau's signs became positive. During the chronic stages, the condition is best controlled by the administration of calcium lactate (30 grains) four or five times a day together with two teaspoonfuls of cod-liver oil once daily. The serum calcium should not be lower than 8 mgm. per 100 cc. of blood serum. In the more severe cases parathormone must also be administered. The dosage should be small (5 units daily) because the use of larger doses for long periods of time is probably dangerous.—E. L.

The functional pathology of hyperparathyroidism. Bulger, H. A., H. H. Dixon, D. P. Barr and O. Schregardus, J. Clin. Investigation, **9**: 143. 1930.

A study of three cases of hyperparathyroidism, two with osteitis fibrosa cystica and the other with multiple myeloma, has presented certain abnormalities of calcium and phosphorus metabolism. Most characteristic of these were a high serum calcium, possibly accounting for many of the clinical features, and an excessive excretion of calcium by the kidneys, apparently explaining the urinary tract complications. The increase of calcium in the urine was sufficient to cause a negative calcium balance, although two patients showed, in addition, an excessive output in stools. Low serum phosphorus was repeatedly found except in one patient with marked kidney insufficiency. Altered phosphorous metabolism was encountered but no specific abnormality presented. There was no indication that the total nitrogen metabolism or creatinine metabolism is abnormal in hyperparathyroidism. Although there were marked changes in calcium and phosphorus, other serum electrolytes were normal. By the administration of orthophosphate it was possible to cause an increase in the serum phosphate, a decrease in serum calcium, a reduction of the calcium in the urine to normal and establish a positive calcium balance. It appears, however, that a continuation of this procedure resulted in an excessive output of calcium in the stools. Following parathyroidectomy in two patients the disturbances of calcium and phosphorus metabolism were reversed. The calcium almost disappeared from the urine and large amounts of calcium and phosphorus were retained in the proportion in which they occur in the bone. One patient reverted to tetany which was almost fatal. It was controlled with difficulty by the administration of large amounts of parathormone and calcium. The metabolism of hyperparathyroidism differs almost completely from that of osteomalacia. In the literature, however, great confusion exists in nomenclature. Cases have been called osteomalacia which probably were examples of hyperparathyroidism. This state is perhaps most often seen with von Recklinghausen's disease of bones, but accompanies hyperplasia of the parathyroid from a variety of causes which include multiple myeloma, extensive carcinoma of bone and possibly other destructive bone processes. These studies indicate that improvement in the clinical state of hyperparathyroidism may be accomplished by the administration of orthophosphate. The possible dangers of such a procedure have been made evident. It would appear that the only effective method of treatment is the removal of parathyroid tissue.—Authors' Summary.

The effect of long continued parathyroid administration upon the body calcium and phosphorus of albino rats. Day, P. L., J. Nutrition, **3**: 157. 1930.

Growing rats receiving an adequate diet were given 15 Hanson units parathyroid extract (0.1 cc. Paroidin) daily from 28 to 60 days of age, at which time they were killed and the entire animals analyzed for calcium and phosphorus. In a second series the rats were given 15 Hanson units parathyroid twice daily from 21 to 60 days of age. Suitable normal controls were also killed and analyzed. The percentages of calcium and phosphorus in the rats receiving parathyroid were not measurably different from the percentages of these elements in untreated rats of the same age, sex and litter.

—Author's Abst.

Vitamin D administration in parathyroid deficiency following thyroidectomy. Hansman, F. S., M. J. Australia, **2**: 809. 1930. Abst., Arch. Physical Therapy, **12**: 125.

After a careful and comprehensive review of this subject, the author summarizes his findings under four headings: Subsequent to thyroidectomy or to excessive radiotherapy to the thyroid gland the following symptoms may develop as a manifestation of parathyroid imbalance: Tetany, cramps, numbness, tingling sensation, a feeling of "pins and needles," grave depression, pronounced irritability, cravings for food, excessive appetite, marked gain in weight, pallor, undue fatigue. Control experiments definitely rule out the possibility of these symptoms being due to hypothyroidism. All these symptoms disappear on the administration of relatively large doses of irradiated ergosterol. Six cases are recorded which illustrate the remarkable response to vitamin D given as "radiostol."

The effect of irradiated ergosterol on thyroparathyroidectomized dogs. Jones, J. H., M. Rapoport and H. L. Hodes, J. Biol. Chem. **86**: 267. 1930.

Preoperative administration of irradiated ergosterol prolongs the life and either prevents or delays the onset of tetany in the thyroparathyroidectomized dog. If tetany occurs, the attacks are usually mild. The daily administration of 10 mgm. of irradiated ergosterol to normal dogs produces a marked hypercalcemia within 2 weeks. The hypercalcemia is invariably accompanied by a loss of appetite. Irradiated ergosterol has no constant effect on the concentration of inorganic phosphorus in the serum. A marked hypercalcemia can be rapidly produced in parathyroidectomized dogs by the administration of large doses of irradiated ergosterol. Dogs from which the parathyroids have been removed can be kept alive indefinitely and apparently in good health by repeated dosage with irradiated ergosterol. Hemoglobin determinations showed no blood concentration accompanying the hypercalcemia produced by overdoses of irradiated ergosterol. No signs of increased viscosity were observed. The differences between the hypercalcemias of irradiated ergosterol and parathormone are discussed. These data show that it is possible to produce a hypercalcemia by feeding large amounts of irradiated ergosterol to parathyroidectomized dogs. In all probability the antirachitic factor does not act by simply stimulating the parathyroid glands to greater activity.

—Authors' Summary.

Hyperparathyroidism: Clinical picture in far advanced stage. Quick, A. J. and A. Hunsberger, Jr., J. A. M. A. **96**: 745. 1931. Abst., A. M. A.

The authors present a case of osteitis fibrosa cystica in which a large physiologically active parathyroid tumor was found and removed. The pathologic process had advanced to such a stage that some of the bones appeared to be almost completely demineralized. Before the onset of the symptoms the patient was a well developed youth, 6 feet tall, and weighing about 200 pounds. At the time of his admission to the hospital he was in fairly good health. Physical examination showed extreme deformity. With the exception of his head, hands and feet, every portion of his skeletal system was distorted and misshapen. The contraction deformities had reduced his total length to 45 inches from his original height of 70 inches. There was a pronounced bulging of the thorax, and both legs just below the knees were bent sharply outward, producing a typical frog-leg appearance. He was, however, relatively well nourished and had no cough, cyanosis or anemia. Respiration was somewhat rapid and shallow because of the deformity of the chest. A parathyroid tumor was found, and after its removal marked improvement was noted. The

importance of early diagnosis is emphasized and a review made of the most common early symptoms and laboratory observations. The relation of vitamin D to the parathyroid is discussed. The use of viosterol is advocated for preventing or minimizing parathyroid tetany, and also for hastening the recalcification of bone after the removal of a parathyroid tumor.

Some problems in the diagnosis and treatment of thyrotoxicosis. Ball, F. E., Am. J. M. Sc. **180**: 687. 1930.

Some of the problems encountered in the diagnosis and treatment of thyrotoxicosis are discussed and illustrated by case histories. Attention is called to the fact that occasionally thyrotoxicosis may be present preceding a rise in the basal metabolism. Such cases may easily be overlooked unless followed for a period of time. Hypometabolism and myxedema are two different things and should not be confused. One is a laboratory diagnosis and the other is a clinical diagnosis. There is a group of patients with myxedema, following thyroidectomy, which cannot be relieved by thyroid therapy. Three cases of persistent thyrotoxicosis with hyperplasia of the remaining thyroid tissue are discussed. A persistent thyrotoxicosis may exist where no thyroid tissue can be demonstrated.—Author's Abst.

Ichthyosis and the thyroid (Ictiosis y Tiroides). Bonilla, E., Actualidad med. **1**: 151. 1929.

A description is given of a typical case of ichthyosis in which the symptoms, including the basal metabolism, did not admit of a hypothyroid diagnosis. The condition was completely cured by thyroid therapy. The author concludes, contrary to a number of writers, that there is neither sufficient clinical or experimental evidence to prove a causal dependency between ichthyosis and thyroid insufficiency, even though many cases appear to improve under treatment.—Author's Abst.

On the endemic goiter-cretinic centers in Sicily (Osservazioni sui focolai di endemia gozzo-cretinica in Sicilia). Coppola, A., Riv. di pat. nerv. **35**: 232. 1930.

The article is a detailed report of cases spread all over the mountainous regions of Sicily. The author insists on the benefits obtained through iodine and opotherapic treatment. Even old, greatly developed goiters respond favorably to the treatment, and no case of "Basedowification" was ever observed.
—G. V.

Myxedema heart with report of one case. Davis, J. C., Ann. Int. Med. **4**: 733. 1931.

The patient had typical myxedema with enlargement of the heart. The electrocardiogram was not normal. The administration of digitalis did not decrease the size of the heart. The administration of 50 grains of thyroid extract was followed by a decrease in the size of the heart and a return of the electrocardiogram to normal.—E. L.

The thyroid in acute polyarticular rheumatism (La tiroidina en el reumatismo poliarticular agudo). Duque Sampayo, A. and López Morales, Rev. méd. de Barcelona, **9**: 470. 1928.

Vincent observed some time ago that in many cases of acute polyarticular rheumatism there occur slight hyperthyroid reactions which manifest themselves with a transitory or prolonged congestion and swelling of the thyroid. Vincent, observing evident improvement, recommends in the prolonged rheumatic cases where there is an absence of the thyroid sign, the administration of thyroid. The authors have treated various cases of polyarticular rheumatism with great success by salicylate with thyroid. This permits, as is demonstrated by a study of basal metabolism, much greater doses of thyroid than can be tolerated otherwise without any symptom of hyperthyroidism. They have also found that with the thyroid treatment alone definite improvements in rheumatism are produced.—E. B.

Pregnancy complicating hyperthyroidism and following thyroidectomy. Fahrni, G. S., Canad. M. A. J. **23**: 645. 1930.

This paper deals with the management of (1) women who become pregnant while suffering from hyperthyroidism and (2) women who become pregnant within two years after thyroidectomy. In a group of women on whom a thyroidectomy was done early in pregnancy, favorable results were obtained from the standpoint of both the mother and foetus. Over a period of five years careful records were obtained of all women who became pregnant within two years after thyroidectomy. In the whole series there were seventy-three women, eight of whom became pregnant a second time within two years following thyroidectomy. There were also four pairs of twins which makes a total of eighty-five babies. In the whole group of women only one died, of eclampsia following confinement; she had been operated on for thyroidectomy for exophthalmic goiter eighteen months before and had made a good recovery. Six babies died, one stillborn at seven and a half months, two (twin pregnancy) died following birth at six months gestation, the premature birth being due to placenta praevia. The remaining three infant deaths were attributed to difficult birth. All the babies, including the six that died, were free from congenital deformity such as monstrosities or other physical disfigurement. The author calls attention to the fact that this tends to refute the statements made by some that there is a tendency to monstrosities among the children born from mothers who have recently undergone thyroidectomy. In the treatment of early pregnancy in a case of acute hyperthyroidism the author advises thyroidectomy after thorough preparation for operation. In his series these women reacted well to thyroidectomy and then went through their pregnancy with little difficulty.—Author's Abst.

Nephric syndromes of thyroid origin (Sindromes nefroides, de origen tiroideo). Jimenez, D., Rev. méd. de Barcelona, **12**: 129. 1929.

The author believes that a hypothyroid factor is involved in fatty degeneration of the kidney. Experimentally he has observed a globulin-hypoalbuminosis of the plasma without modification of the relation of the albumen globulin to cholesterin of the blood. Administration of thyroxine produces entirely different results. Realizing the possibility of other factors he produced, in addition to thyroidectomy, liver lesions by chloroform intoxication. The results are not decisive enough to prove that effects are the result of a thyroid-liver insufficiency, but it is very similar according to the author.—E. B.

Our method of Roentgen ray treatment of exophthalmic goiter in older women (Unsere methode der Roentgenbehandlung der basedowschen krankheit. Bei aelteren frauen). Jugenburg, A., Strahlentherapie, **36**: 491. 1930. Abst., Arch. Physical Therapy, **11**: 504.

Graves' disease in older women is distinguished by its particularly severe course. The imbalance in the endocrine system is due to lesions of the ovaries, thyroid gland and hypophysis. The method of irradiation of women affected by exophthalmic goiter at the age of over 40 years consists in the irradiation of the thyroideal and thymic regions as well as of the pituitary gland. In those cases in which no improvement occurs after the first irradiation of the thyroid region, irradiation of the pituitary gland is indicated. The latter procedure is also to be observed in those younger women affected by exophthalmic goiter wherein hyperfunction of the pituitary gland, due to whichever physiologic process (pregnancy) is a concomitant factor.

Thyroid as a mordanting agent (La opoterapia tiroides como mediacion mordiente). Marañon, G., Med. ibera. **1**: 57. 1929.

Hypothyroid organisms are capable of extraordinary assimilation, so much so that they may gain weight even on minimum rations. Hyperthyroidism gives the opposite effect. Persons with mediocre thyroid function are more sensitive to certain drugs such as opium, quinine and aspirin. By use of thyroid larger doses of these drugs may be administered. A combination with quinine is used for vertigo. Of particular interest is the facility with which intolerance for salicylate is suppressed. This is of considerable importance since this agent is used in the treatment of polyarticular rheumatism. There are undoubtedly other applications not mentioned.—E. B.

Contribution to the study of the effect of hyperthyroidism on temperature (Contribucion al estudio del comportamiento de la temperatura en el hipertiroidismo). Marañon, G. and E. Bonilla, Med. ibera, **1**: 113. 1928.

Hyperthyroidism of all kinds frequently presents a tendency to increased temperature, almost always in a form of a prolonged fever. It is believed that hyperthyroidism produces an unstable thermal condition which is revealed by the response to usual pyrogenic causes. In a high percentage of cases of hyperthyroidism with fever, the existence of latent infections has been shown to exist. In hyperthyroidism the final reaction brought on by focal infection becomes particularly turbulent and insistent. It is not denied that the hyperthyroid condition without infection is capable of producing the rise in temperature, but when hypothyroidism and fever occur simultaneously one should seek a focal infection. Of the seventeen cases studied, nine showed rapid increase in temperature as determined by axillary and rectal temperatures, at varying periods after a brisk 1500-meter walk. Among the nine, four showed latent septic foci. Two of the seventeen showed the sign of Lucatell. After the exercise the temperature increases more or less as in normal individuals just when the initial temperature in response is normal, as when there is rapid hyperthermia.—E. B.

Further researches on lymph-adenoid goitre in rats. McCarrison, R., Indian J. M. Research, **18**: 577. 1930.

The experimental production of lymph-adenoid goitre in rats, by means of a diet composed of white bread and dried yeast, is confirmed. The average urinary excretion of iodine by rats fed on this diet was 0.075 mgm. per litre. Rats fed on this diet are more likely to develop lymph-adenoid goitre during the spring and summer than during the autumn and winter. It is considered that the seasonal incidence of the condition is not determined by the action of temperature per se on the thyroid gland. The addition of slaked lime to the diet of white bread and yeast had no influence on the incidence of the goitres caused by this diet, though it appeared to augment the size of those occurring during the summer months; its addition to the diet during the winter months did not cause an increase in size of the thyroid gland. The addition of iodine to this diet appeared to increase the incidence of lymph-adenoid goitre in the spring and summer, but not in the autumn and winter experiments. This condition was most common in rats to whose diet iodine was added and whose urinary excretion of iodine averaged 0.122 mgm. per litre. A description of four representative specimens of experimentally-produced lymph-adenoid goitre in rats is provided by Drs. Williamson and Pearse, who originally described this condition in man. The experimentally-produced lymph-adenoid goitre is identical with that occurring in man. The faults common to the diets hitherto used in the experimental-production of lymph-adenoid goitre are: (a) deficiency of fat-soluble vitamins (A and D); and (b) deficiency of vitamin C. Rats fed on synthetic diets deficient in vitamin C, but complete in other respects, did not develop lymph-adenoid, or other goitre. Lymph-adenoid goitre occurred in 2 out of 18 rats fed on a diet having the above faults, although they were exposed daily to the direct rays of the sun, and were, presumably, acquiring a sufficiency of vitamin D in this way. The average urinary excretion of iodine by rats so treated was 0.096 mgm. per litre. By a process of exclusion of other vitamins, vitamin A-deficiency would appear to be the chief dietetic factor concerned in causing lymph-adenoid goitre in rats; but further experimentation is necessary before the relative importance of the fat-soluble vitamins (A and D) can be finally determined. It is pointed out that while vitamin-deficiency appears to be the main dietetic factor in causing lymph-adenoid goitre in rats—without which it has not up to the present been observed to arise—the possibility has to be borne in mind that some unknown positive agency may be associated with the negative one of vitamin-deficiency in the causation of this type of goitre. It would appear from the results of these experiments that in the absence of a sufficiency of fat-soluble vitamins in the diet the thyroid gland is unable to deal with iodine in a normal way; and that its administration in these circumstances may actually favour goitre-production. It seems possible that the varying results of iodine-prophylaxis in different individuals may be related to the varying amounts of these vitamins in the diets.—Author's Summary.

The effects of high protein diets on the thyroid gland. McCarrison, R. and K. B. Madhava, Indian J. M. Research, **18**: 1. 1930.

A high concentration of animal protein in the diet did not cause thyroid enlargement in growing rats living under conditions of perfect cleanliness. Burgest's observation (1917) is thus confirmed. This result was observed both in animals whose diets were rich in fat-soluble vitamins and in those whose diets were poor in these factors. It was observed also in rats whose diets were rich in iodine and whose urinary excretion of iodine was very high as well as in those whose diets were relatively poor in iodine. The general effect of the experimental diets was to cause the thyroid gland to be smaller than normal; the amount of animal protein, or iodine and of fat-soluble vitamins in the diets did not materially contribute to this result. A less common effect of the experimental diets was to cause thyroid enlargement. This effect was definitely related to deficiency of fat-soluble vitamins especially in diets having a low content of animal protein. It was not related to an insufficient absorption of iodine. While deficiency of fat-soluble vitamins was the main dietetic factor concerned in causing thyroid enlargement—and without which such enlargement did not occur—it was not the only factor concerned. The existence of an unknown positive goitrogenic agency is postulated, in addition to the known negative one of vitamin-deficiency. This positive agency was not insanitation; it may have been "infection." High protein diets had a marked effect in increasing the volume of urine excreted. They gave rise to albuminuria even in animals whose diets contained a sufficiency of fat-soluble vitamins. High protein diets appeared to stimulate the excretion of iodine in the urine, and this stimulation seemed to be effected by the protein increasing the volume of urine. The ingestion of large amounts of animal protein, in association with an insufficiency of vitamin A, was very prone to cause disease of the urinary, the respiratory and the gastrointestinal tracts.—Authors' Summary.

The nature of Graves' disease. Moschowitz, E., Arch. Int. Med. **46**: 610. 1930.

A paper on the causal relationships in the mechanism of Graves' syndrome. The condition described during the world war as neurocirculatory asthenia and the clinical picture presented by many "neurotic" young men and women are largely phases or degrees of susceptibility to or the existence of Graves' disease since they possess the common denominator—the significant neuropathic personality. The fully developed Graves' syndrome is merely one phase of a process, the natural history of which extended long before and projected long after the time of actual diagnosis of the disease. Acquaintance with a number of persons for years preceding the development of Graves' disease reveals in them personal characteristics that describe the so-called Graves' constitution. Almost throughout life these persons are sanguine, sensitive, restless, temperamental, emotional and present brilliant eyes, rapid pulse, and slight tremor, all of which are occasionally described by others as forme frustes, autonomic imbalance, or the pre-Basedow state. A psychic insult may suddenly lead to the complete picture of Graves' syndrome. Despite apparent improvement following thyroidectomy, the personality of the patient, i.e., the Graves' constitution, never disappears. Hence, according to Moschowitz, a patient with Graves' disease is never completely cured. The exciting cause of the syndrome is almost invariably of psychic nature, such as fear or a sudden emotional crisis. While in occasional instances infections may seem to play an exciting rôle, some doubt may be attached to this factor per se since fear may be associated with infection. A thymicolymphatic constitution may coexist with Graves' syndrome, but there is no evidence that the thymus gland is causally related to thyroid activity. Also, while the thyroid function appears excessive in Graves' syndrome it likewise appears that this is secondary; indeed, thyroid hyperplasia is frequently absent. Basal metabolism determinations merely indicate the degree of thyroid participation and do not serve as an important diagnostic sign of Graves' syndrome. Recognition of the relation of the constitution to Graves' syndrome will explain the many failures in treatment. An important element in therapeusis is the alteration of the basic constitution, and this in turn requires environmental adjustment.

—I. B.

The glycosuria of hyperthyroidism and its clinical significance. Rabinowitch, I. M., Ann. Int. Med. **4**: 881. 1931.

The author by applying Allen's paradoxical law (the more sugar given to a non-diabetic the more is utilized) has been able to distinguish between the true diabetic and the other forms of glycosuria. Simultaneous respiratory metabolism determinations and blood sugar times curves are helpful.—E. L.

The therapeutic use of thyroid derivatives. Rose, E., Pennsylvania M. J. **34**: 235. 1931.

The author concludes that desiccated thyroid gland and thyroxin are similar in their physiologic effect. It is sometimes necessary to substitute one preparation for the other in order to obtain satisfactory therapeutic results. Response to treatment is not always reflected equally in the signs and symptoms of the condition under treatment. Among the conditions responsive to thyroid therapy, hypothyroid states and certain types of simple goiter are most important; others include obesity with low basal metabolism, anorexia nervosa, lipoid nephrosis, certain obscure types of edema, and heart block.—I. B.

Myxedema with cerebellar symptoms: Case. Rud, E., Hospitalstidende, **73**: 25. 1930. Abst., J. A. M. A. **94**: 1882. 1930.

In Rud's instance of myxedema in a man, aged 69, it is believed that the condition originated on an arteriosclerotic basis, roentgen examination having established calcifications in the superior thyroid artery. The marked cerebellar symptoms—asynergy, dysmetria, ataxia and adiadokokinesis—yielded to treatment with thyroidin.

Clinical studies of Basedow's disease in children (Etude clinique de la maladie de Basedow chez l'enfant). Schereschewsky, N. A., Rev. franç. d'endocrinol, **7**: 456. 1929.

A case in a 12-year-old girl is reported. There was a retarding of psychic as well as of sexual development. Satisfactory methods of treatment are yet to be proposed.—B. C.

The diagnosis of hyperthyroidism. Snowden, R. R., Pennsylvania M. J., **34**: 233. 1931.

The most constant and typical signs presented by a case of uncomplicated, active hyperthyroidism are tachycardia, tremor, and loss of weight. When all three of these signs are found, the chances are about 40 to 1 that hyperthyroidism is present. The more common sources of error in diagnosis can best be avoided if the physician bases his conclusions on reliable and accurate observations made over a period of time, varying from weeks to months as indicated.—I. B.